```
* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  SEP 09   ACD predicted properties enhanced in REGISTRY/ZREGISTRY
 NEWS  4  OCT 03   MATHDI removed from STN
 NEWS  5  OCT 04   CA/CAplus-Canadian Intellectual Property Office (CIPO) added
                   to core patent offices
 NEWS  6  OCT 13   New CAS Information Use Policies Effective October 17, 2005
 NEWS  7  OCT 17   STN(R) AnaVist(TM), Version 1.01, allows the export/download
                   of CAplus documents for use in third-party analysis and
                   visualization tools
 NEWS  8  OCT 27   Free KWIC format extended in full-text databases
 NEWS  9  OCT 27   DIOGENES content streamlined
 NEWS 10  OCT 27   EPFULL enhanced with additional content
 NEWS 11  NOV 14   CA/CAplus - Expanded coverage of German academic research
 NEWS 12  NOV 30   REGISTRY/ZREGISTRY on STN(R) enhanced with experimental
                   spectral property data
 NEWS 13  DEC 05   CASREACT(R) - Over 10 million reactions available
 NEWS 14  DEC 14 2006 MeSH terms loaded in MEDLINE/LMEDLINE
 NEWS 15  DEC 14 2006 MeSH terms loaded for MEDLINE file segment of TOXCENTER
 NEWS 16  DEC 14 CA/CAplus to be enhanced with updated IPC codes
 NEWS 17  DEC 16 MARPATprev will be removed from STN on December 31, 2005

 NEWS EXPRESS  DECEMBER 02 CURRENT VERSION FOR WINDOWS IS V8.01,
               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 02 DECEMBER 2005.
               V8.0 USERS CAN OBTAIN THE UPGRADE TO V8.01 AT
               http://download.cas.org/express/v8.0-Discover/

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
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  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 11:22:18 ON 19 DEC 2005

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'REGISTRY' ENTERED AT 11:22:30 ON 19 DEC 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
```

provided by InfoChem.

STRUCTURE FILE UPDATES: 18 DEC 2005 HIGHEST RN 870123-57-2
DICTIONARY FILE UPDATES: 18 DEC 2005 HIGHEST RN 870123-57-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

```
**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
**********************************************************************
```

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

```
=>
Uploading structure

L1      STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1              STR

=> s l1
SAMPLE SEARCH INITIATED 11:29:01 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -   215510 TO ITERATE

  0.9% PROCESSED     2000 ITERATIONS                          24 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **INCOMPLETE**
                        BATCH   **INCOMPLETE**
PROJECTED ITERATIONS:      4283065 TO  4337335
PROJECTED ANSWERS:           48672 TO    54772

L2           24 SEA SSS SAM L1

=>
Uploading structure

L3      STRUCTURE UPLOADED
```

```
=> d l3
L3 HAS NO ANSWERS
L3              STR

=> s l3
SAMPLE SEARCH INITIATED 11:31:08 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -   102859 TO ITERATE

  1.9% PROCESSED     2000 ITERATIONS                                43 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **INCOMPLETE**
                        BATCH   **INCOMPLETE**
PROJECTED ITERATIONS:      2038173 TO  2076187
PROJECTED ANSWERS:           41409 TO    47049

L4           43 SEA SSS SAM L3

=>
Uploading structure

L5      STRUCTURE UPLOADED

=> d l5
L5 HAS NO ANSWERS
L5              STR

=> s l5
SAMPLE SEARCH INITIATED 11:37:27 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -    24321 TO ITERATE

  8.2% PROCESSED     2000 ITERATIONS                                12 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:       477090 TO   495750
PROJECTED ANSWERS:            2194 TO     3642

L6           12 SEA SSS SAM L5

=> s l5 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 160.90 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 11:37:34 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   484852 TO ITERATE

100.0% PROCESSED   484852 ITERATIONS                            3264 ANSWERS
SEARCH TIME: 00.00.02

L7         3264 SEA SSS FUL L5

=> file hcaplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                             174.66     174.87

FILE 'HCAPLUS' ENTERED AT 11:41:56 ON 19 DEC 2005
```

FILE COVERS 1907 - 19 Dec 2005 VOL 143 ISS 26
FILE LAST UPDATED: 18 Dec 2005 (20051218/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l7
L8 37147 L7

=> s l8 and bell, r?/au
2688 BELL, R?/AU
L9 3 L8 AND BELL, R?/AU

=> d l9, ibib abs hitstr, 1-3

L9 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1993:420427 HCAPLUS
DOCUMENT NUMBER: 119:20427
TITLE: The effects of D-fenfluramine on the development of aflatoxin-B1 induced GGT+ hepatic foci in F344 rats
AUTHOR(S): **Bell, Rhonda C.**; Levitsky, David A.; Campbell, T. Colin
CORPORATE SOURCE: Div. Nutr. Sci., Cornell Univ., Ithaca, NY, 14853, USA
SOURCE: International Journal of Obesity (1993), 17(4), 215-21
CODEN: IJOBDP; ISSN: 0307-0565
DOCUMENT TYPE: Journal
LANGUAGE: English

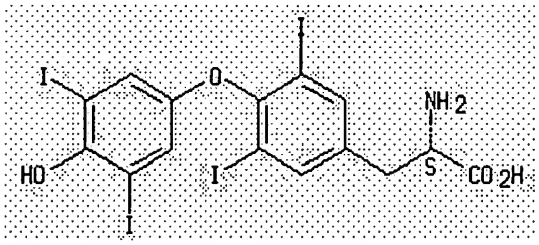
AB The role of total caloric intake and attained body wt. in the carcinogenic process in rodents is controversial. In the present study, the authors examd. the development of hepatic pre-neoplastic foci in rats treated with aflatoxin-B1 (AFB) and given the drug D-fenfluramine (FEN). Ingestion of this drug leads to a redn. in body wt. by increasing the thermogenic response to a meal and by transiently reducing food intake. Young male rats were dosed with AFB or vehicle alone and were then assigned to receive control diet (NO FEN) or control diet + FEN (FEN; 0.15 g/kg diet) for 12-14 wk. Body wt. gain and food intake were reduced among animals given FEN; brown adipose tissue wt. (% body wt.) was elevated in these groups. Indexes of protein status, and concns. of T3, T4 and insulin did not differ among the groups. All animals given FEN developed GGT+ hepatic foci. The no. and vol. fraction of foci were significantly larger in FEN relative to NO FEN animals. The mean diam. of foci was slightly enhanced

among FEN animals. These results suggest that FEN promotes the development of AFB-induced hepatocellular foci, despite reduced food intake and lower body wt. Since FEN is widely used as a wt. loss aid, these findings deserve further study.

IT **51-48-9P**, Thyroxine, biological studies **6893-02-3P**, Triiodothyronine
RL: BIOL (Biological study); PREP (Preparation)
(fenfluramine effect on, of blood plasma, carcinogenesis from aflatoxin-B1 enhancement in relation to)

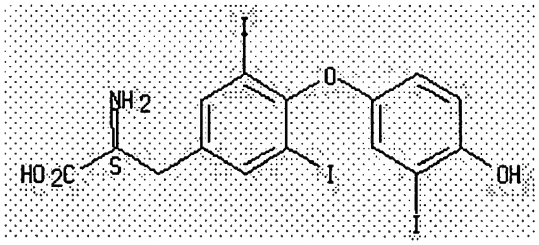
RN 51-48-9 HCAPLUS
CN L-Tyrosine, O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 6893-02-3 HCAPLUS
CN L-Tyrosine, O-(4-hydroxy-3-iodophenyl)-3,5-diiodo- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L9 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

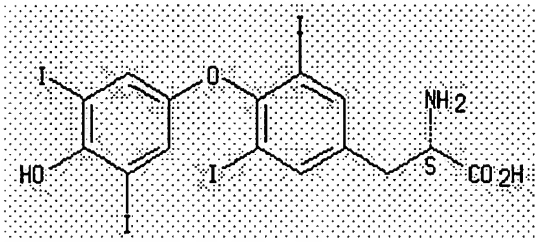
ACCESSION NUMBER: 1974:24493 HCAPLUS
DOCUMENT NUMBER: 80:24493
TITLE: Serum tests for thyroid function
AUTHOR(S): **Bell, Robert L.**
CORPORATE SOURCE: Parkview Hosp., Nashville, TN, USA
SOURCE: Journal of the Tennessee Medical Association (1973), 66(7), 626-7
CODEN: JTMAAM; ISSN: 0040-3318
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Thyroid activity cannot be reliably estd. by protein bound I (PBI) because of the intake of I in salt, food, H2O, and x-ray diagnostics. Oral contraceptives produce increased thyroid binding globulin, which further elevates PBI. The triiodothyronine (T3) binding test, while excellent for hyperthyroidism, can be misleading in hypothyroidism. A free thyroxine (T4) index using a resin T4 uptake procedure and a T4 detn. by the Murphy-Potter method was more helpful than PBI, T3, or T3 binding studies.

IT **51-48-9**, analysis
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in blood serum, thyroid function in relation to)

RN 51-48-9 HCAPLUS
CN L-Tyrosine, O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



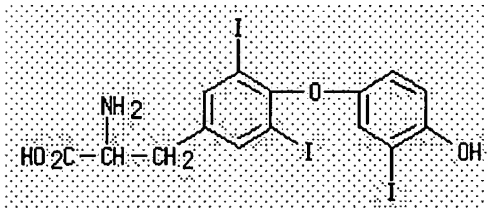
L9 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1961:77442 HCAPLUS
DOCUMENT NUMBER: 55:77442
ORIGINAL REFERENCE NO.: 55:14699c-d
TITLE: Concentration of labeled triiodothyronine and radioactive albumin in human cerebral neoplasms
AUTHOR(S): **Bell, Robert L.**
CORPORATE SOURCE: State Univ. of New York, Brooklyn
SOURCE: J. Nuclear Med. (1960), 1, 180-5
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB The use of labeled triiodothyronine (I) and radioactive serum albumin (II) in the detection and possible destruction of cerebral tumors by radiation was investigated. Both materials were administered intravenously. No significant difference in level of radioactive I was found in human cerebral tumors when compared to normal brain uptake 24 hrs. after its administration. There was significantly greater II uptake by cerebral tumors as compared to normal brain uptake.

IT 3130-96-9, Alanine, 3-[4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]-
(in brain neoplasm after injection)
RN 3130-96-9 HCAPLUS
CN Tyrosine, O-(4-hydroxy-3-iodophenyl)-3,5-diiodo- (9CI) (CA INDEX NAME)



=> his
HIS IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d his

(FILE 'HOME' ENTERED AT 11:22:18 ON 19 DEC 2005)

```
     FILE 'REGISTRY' ENTERED AT 11:22:30 ON 19 DEC 2005
L1              STRUCTURE UPLOADED
L2           24 S L1
L3              STRUCTURE UPLOADED
L4           43 S L3
L5              STRUCTURE UPLOADED
L6           12 S L5
L7         3264 S L5 FULL

     FILE 'HCAPLUS' ENTERED AT 11:41:56 ON 19 DEC 2005
L8        37147 S L7
L9            3 S L8 AND BELL, R?/AU

=> s l8 not l9
L10       37144 L8 NOT L9

=> s l10 and beswick, p?/au
             57 BESWICK, P?/AU
L11           0 L10 AND BESWICK, P?/AU

=> s l10 and gosmini, r?/au
             16 GOSMINI, R?/AU
L12           0 L10 AND GOSMINI, R?/AU

=> s l10 and grimes, r?/au
            557 GRIMES, R?/AU
L13           0 L10 AND GRIMES, R?/AU

=> s l10 and hamlett, c?/au
              2 HAMLETT, C?/AU
L14           0 L10 AND HAMLETT, C?/AU

=> s l10 and king, n?/au
            567 KING, N?/AU
L15           0 L10 AND KING, N?/AU

=> s l10 and patel, v?/au
           1058 PATEL, V?/AU
L16           2 L10 AND PATEL, V?/AU

=> d l16, ibib abs hitstr, 1-2

L16  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2005 ACS on STN
```

Full Text | Citing References

```
ACCESSION NUMBER:         2003:70027  HCAPLUS
DOCUMENT NUMBER:          138:297961
TITLE:                    Isolation and characterization of human thyroid
                          endothelial cells
AUTHOR(S):                Patel, Vimal A.; Logan, Ann; Watkinson, John C.;
                          Uz-Zaman, Saad; Sheppard, Michael C.; Ramsden, James
                          D.; Eggo, Margaret C.
CORPORATE SOURCE:         Division of Medical Sciences, University of
                          Birmingham, Birmingham, B15 2TTL, UK
SOURCE:                   American Journal of Physiology (2003), 284(1, Pt. 1),
                          E168-E176
                          CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER:                American Physiological Society
DOCUMENT TYPE:            Journal
```

LANGUAGE: English

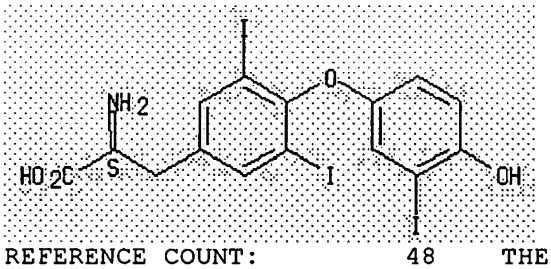
AB From collagenase digests of human thyroid, endothelial cells were sepd. from follicular cells by their greater adherence to gelatin-coated plates. Endothelial cells were further purified using fluorescence-activated cell sorting, selecting for cells expressing factor VIII-related antigen. Isolated cells were neg. for thyroglobulin and calcitonin when examd. by immunostaining. The receptor for the angiopoietins, Tie-2, was expressed by the cells, and expression was increased by agents that elevate cAMP. Nitric oxide synthase (NOS) 3, the endothelial form of NOS, was expressed by the cells and similarly regulated. Cells responded strongly to the mitogen fibroblast growth factor (FGF)-2 in growth assays but only weakly to vascular endothelial growth factor (VEGF). VEGF was, however, able to stimulate nitric oxide release from the cells consistent with their endothelial origin. The FGF receptor (FGFR1) was full length (120 kDa) and immunolocalized to the cytosol and nucleus. TSH did not regulate FGFR1, but its expression was increased by VEGF. Thrombospondin, a product of follicular cells, was a growth inhibitor, but neither TSH nor 3,5,3'-triiodothyronine had direct mitogenic effects. Thyroid follicular cell conditioned medium contained plasminogen activator activity and stimulated the growth of the endothelial cells, but when treated with plasminogen to produce the endothelial-specific inhibitor, angiostatin, growth was inhibited. Human thyroid endothelial cell cultures will be invaluable in detg. the cross talk between endothelial and follicular cells during goitrogenesis.

IT **6893-02-3**, 3,5,3'-Triiodothyronine
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(isolation and characterization of human thyroid endothelial cells)

RN 6893-02-3 HCAPLUS

CN L-Tyrosine, O-(4-hydroxy-3-iodophenyl)-3,5-diiodo- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

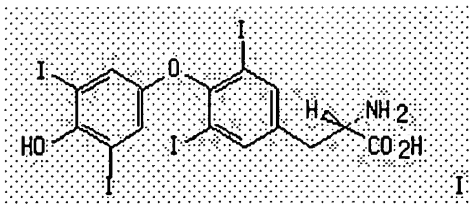


REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1983:149644 HCAPLUS
DOCUMENT NUMBER: 98:149644
TITLE: A method for the estimation of laevothyroxine in bulk and dosage form
AUTHOR(S): Patel, R. B.; Gandhi, T. P.; Shah, G. F.; **Patel, V. C.**; Gilbert, R. N.
CORPORATE SOURCE: Res. Dev. Cadila Lab., Ahmedabad, 380 008, India
SOURCE: Indian Journal of Pharmaceutical Sciences (1982), 44(4), 81-2
CODEN: IJSIDW; ISSN: 0250-474X
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



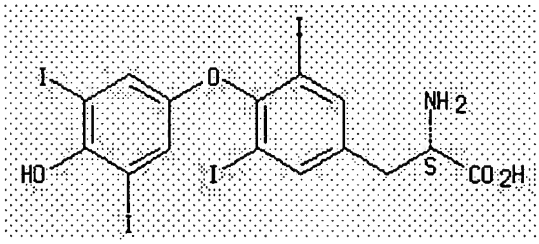
AB L-thyroxine (I) [51-48-9] was detd. in bulk drug and tablets by colorimetric detn. of its complex with 2,4,6-trinitrobenzenesulfonic acid at 423 nm, after extn. into isoBuCOMe. Lamber Beer's law was obeyed at 40-250 μg/mL. This method gives comparable results to the official method and is suitable for routine control even though it is not specific for the L isomer.

IT 51-48-9, analysis
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in bulk and pharmaceuticals by colorimetry)

RN 51-48-9 HCAPLUS

CN L-Tyrosine, O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> file hcaplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	44.30	219.17

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-3.65	-3.65

FILE 'HCAPLUS' ENTERED AT 11:46:49 ON 19 DEC 2005
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 19 Dec 2005 VOL 143 ISS 26

FILE LAST UPDATED: 18 Dec 2005 (20051218/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	2.45	221.62

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-3.65

FILE 'REGISTRY' ENTERED AT 11:46:51 ON 19 DEC 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 18 DEC 2005 HIGHEST RN 870123-57-2
DICTIONARY FILE UPDATES: 18 DEC 2005 HIGHEST RN 870123-57-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

```
**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
**********************************************************************
```

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

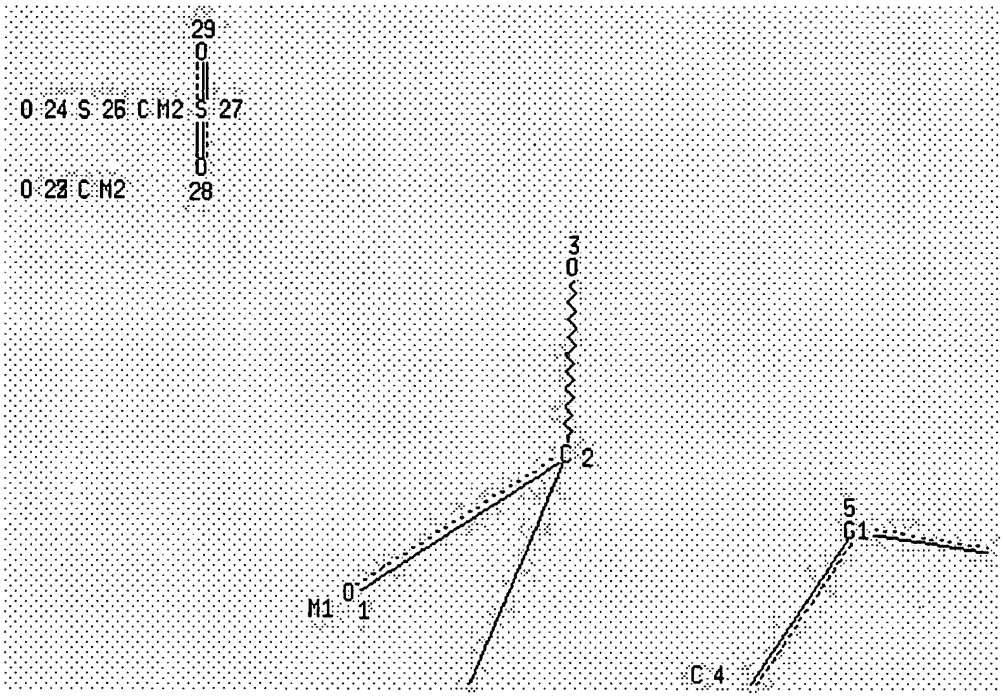
http://www.cas.org/ONLINE/UG/regprops.html

=>
Uploading structure

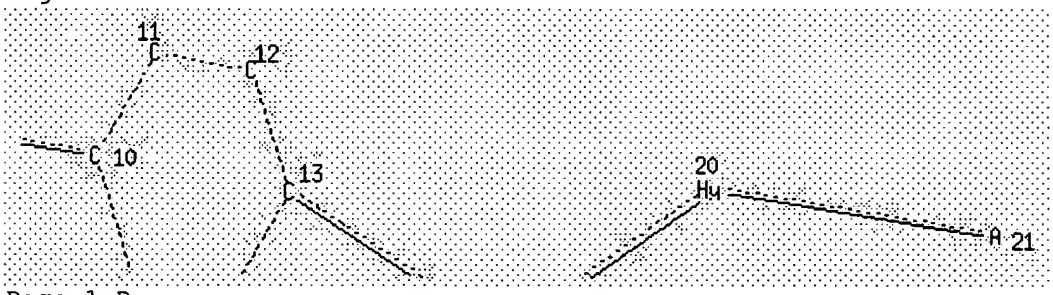
L17 STRUCTURE UPLOADED

=> d l17
L17 HAS NO ANSWERS

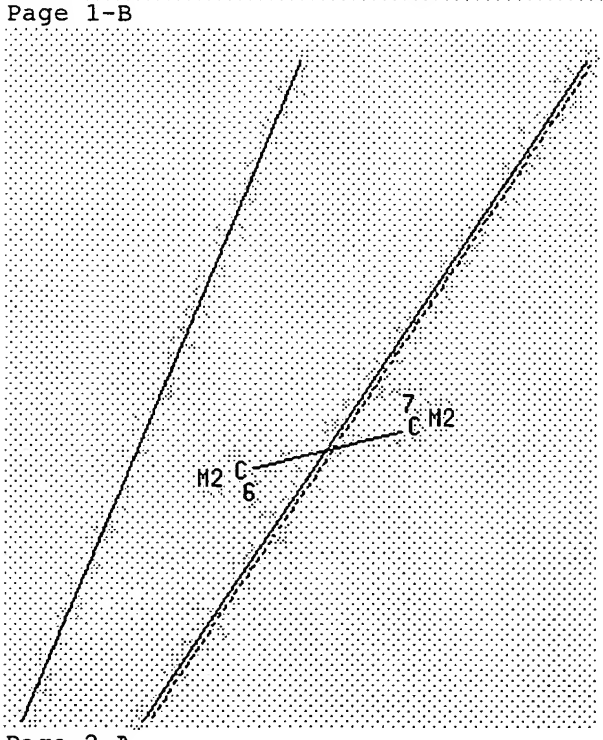
L17 STR



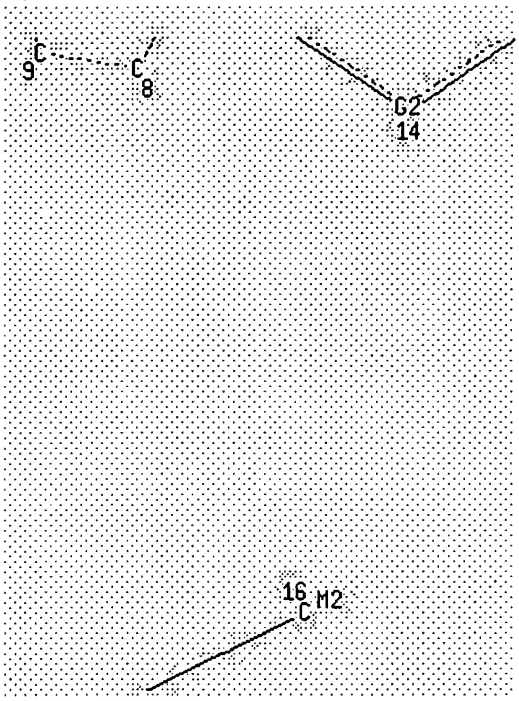
Page 1-A



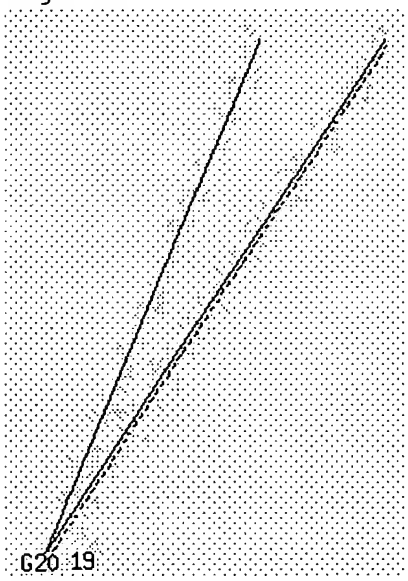
Page 1-B



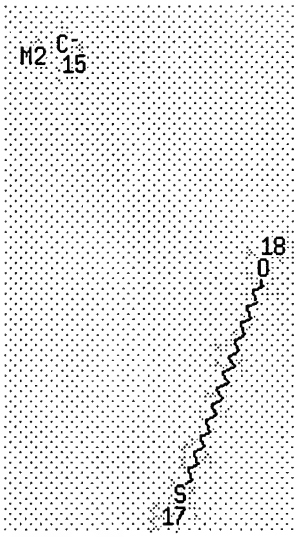
Page 2-A



Page 2-B



Page 3-A




```
Page 3-B
VAR G1=22/23/6-19 6-10
VAR G2=24/25/26/27/15-13 15-20/17-13 17-20
REP G20=(1-2) 4-2 4-5
NODE ATTRIBUTES:
HCOUNT  IS M1     AT   1
HCOUNT  IS M2     AT   6
HCOUNT  IS M2     AT   7
HCOUNT  IS M2     AT  15
HCOUNT  IS M2     AT  16
HCOUNT  IS M2     AT  23
HCOUNT  IS M2     AT  26
NSPEC   IS C      AT   1
NSPEC   IS C      AT   2
NSPEC   IS C      AT   3
NSPEC   IS C      AT   4
NSPEC   IS C      AT   5
NSPEC   IS C      AT   6
NSPEC   IS C      AT   7
NSPEC   IS R      AT   8
NSPEC   IS R      AT   9
NSPEC   IS R      AT  10
NSPEC   IS R      AT  11
NSPEC   IS R      AT  12
NSPEC   IS R      AT  13
NSPEC   IS C      AT  14
NSPEC   IS C      AT  15
NSPEC   IS C      AT  16
NSPEC   IS C      AT  17
NSPEC   IS C      AT  18
NSPEC   IS C      AT  19
NSPEC   IS C      AT  20
NSPEC   IS C      AT  21
DEFAULT MLEVEL IS ATOM
MLEVEL  IS CLASS  AT   1  2  3  4  6  7 15 16 17 18 21 22 23 24 25 26 27
          28 29
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS M1-X3 N  AT  20

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS  29
```

```
STEREO ATTRIBUTES: NONE


=> s l17
SAMPLE SEARCH INITIATED 11:49:00 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -   214737 TO ITERATE

  0.9% PROCESSED     2000 ITERATIONS                                 1 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **INCOMPLETE**
                        BATCH   **INCOMPLETE**
PROJECTED ITERATIONS:      4267651 TO  4321829
PROJECTED ANSWERS:            1526 TO     2768

L18            1 SEA SSS SAM L17

=>
Uploading structure

L19     STRUCTURE UPLOADED

=> d l19
L19 HAS NO ANSWERS
L19              STR
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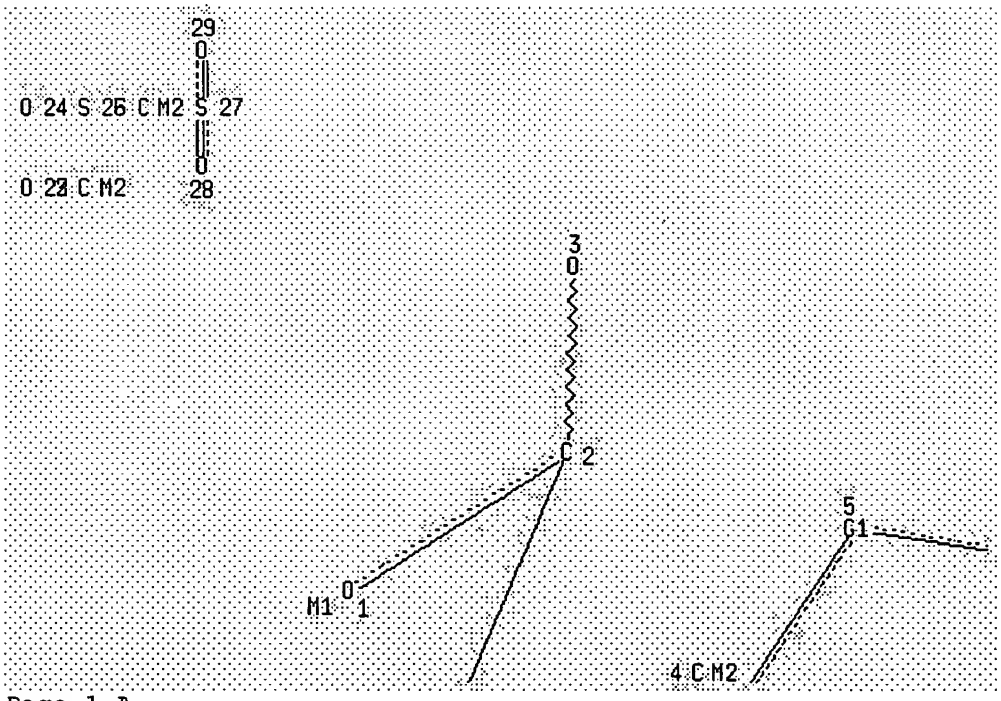
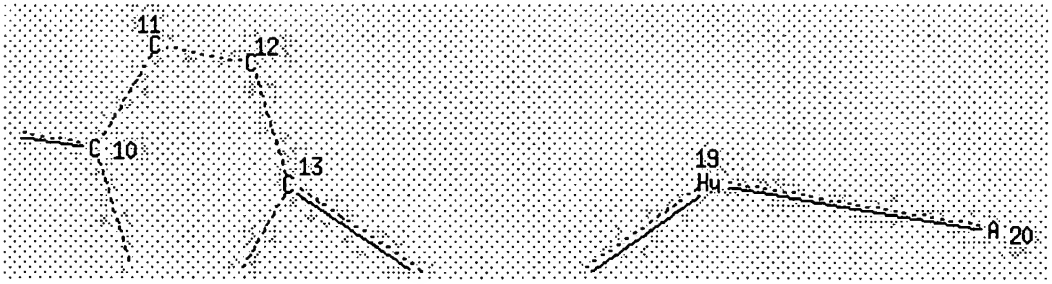
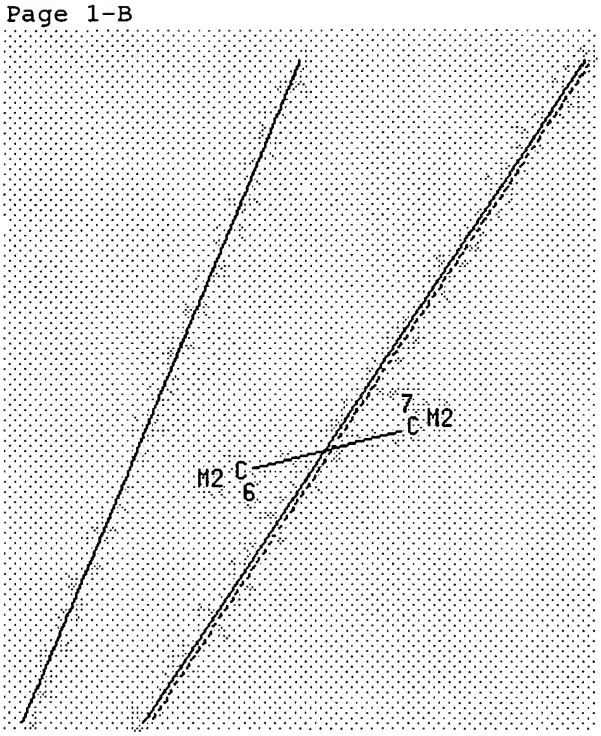


Page 1-A



Page 1-B



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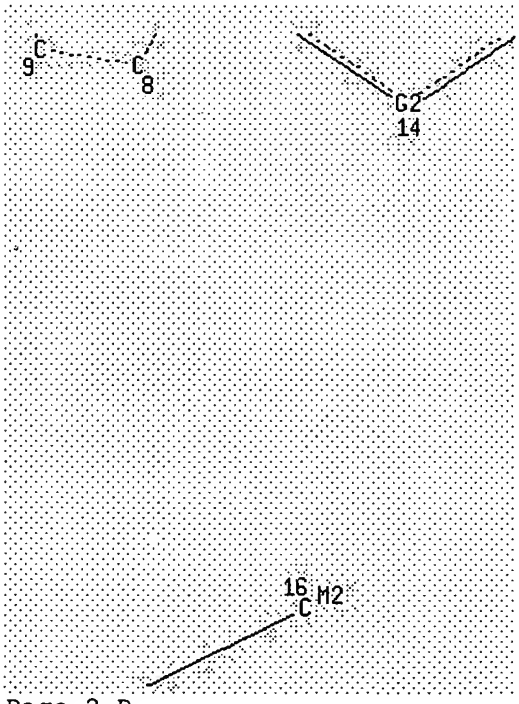

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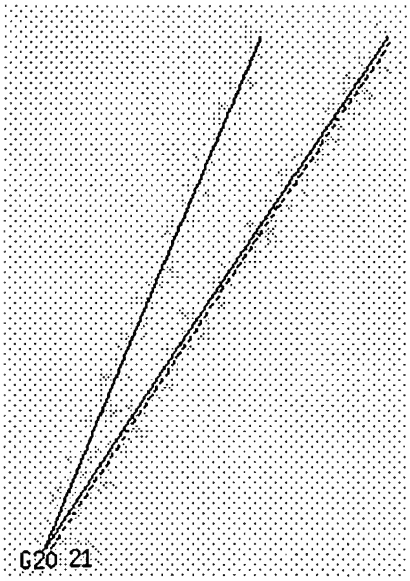
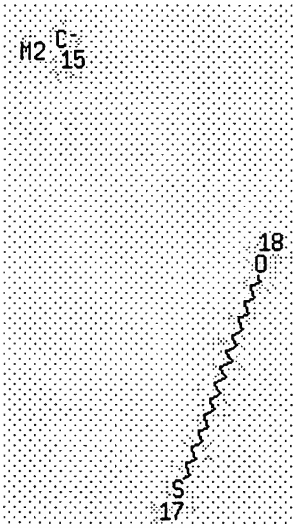


Page 3-A



Page 3-B

```
VAR G1=22/23/6-21 6-10
VAR G2=24/25/26/27/15-13 15-19/17-13 17-19
REP G20=(1-2) 4-2 4-5
NODE ATTRIBUTES:
HCOUNT  IS M1     AT   1
HCOUNT  IS M2     AT   4
HCOUNT  IS M2     AT   6
HCOUNT  IS M2     AT   7
HCOUNT  IS M2     AT  15
HCOUNT  IS M2     AT  16
HCOUNT  IS M2     AT  23
HCOUNT  IS M2     AT  26
NSPEC   IS C      AT   1
NSPEC   IS C      AT   2
NSPEC   IS C      AT   3
NSPEC   IS C      AT   4
NSPEC   IS C      AT   5
NSPEC   IS C      AT   6
NSPEC   IS C      AT   7
NSPEC   IS R      AT   8
NSPEC   IS R      AT   9
NSPEC   IS R      AT  10
```

```
NSPEC   IS R      AT  11
NSPEC   IS R      AT  12
NSPEC   IS R      AT  13
NSPEC   IS C      AT  14
NSPEC   IS C      AT  15
NSPEC   IS C      AT  16
NSPEC   IS C      AT  17
NSPEC   IS C      AT  18
NSPEC   IS C      AT  19
NSPEC   IS C      AT  20
NSPEC   IS C      AT  21
DEFAULT MLEVEL IS ATOM
MLEVEL  IS CLASS  AT   1  2  3  4  6  7 15 16 17 18 20 22 23 24 25 26 27
          28 29
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS M1-X3 N  AT  19

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS  29

STEREO ATTRIBUTES: NONE


=> s l19
SAMPLE SEARCH INITIATED 11:51:33 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -   214737 TO ITERATE

  0.9% PROCESSED     2000 ITERATIONS                                 0 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **INCOMPLETE**
                        BATCH   **INCOMPLETE**
PROJECTED ITERATIONS:      4267651 TO  4321829
PROJECTED ANSWERS:               0 TO        0

L20           0 SEA SSS SAM L19

=>
Uploading structure

L21     STRUCTURE UPLOADED

=> d l21
L21 HAS NO ANSWERS
L21             STR
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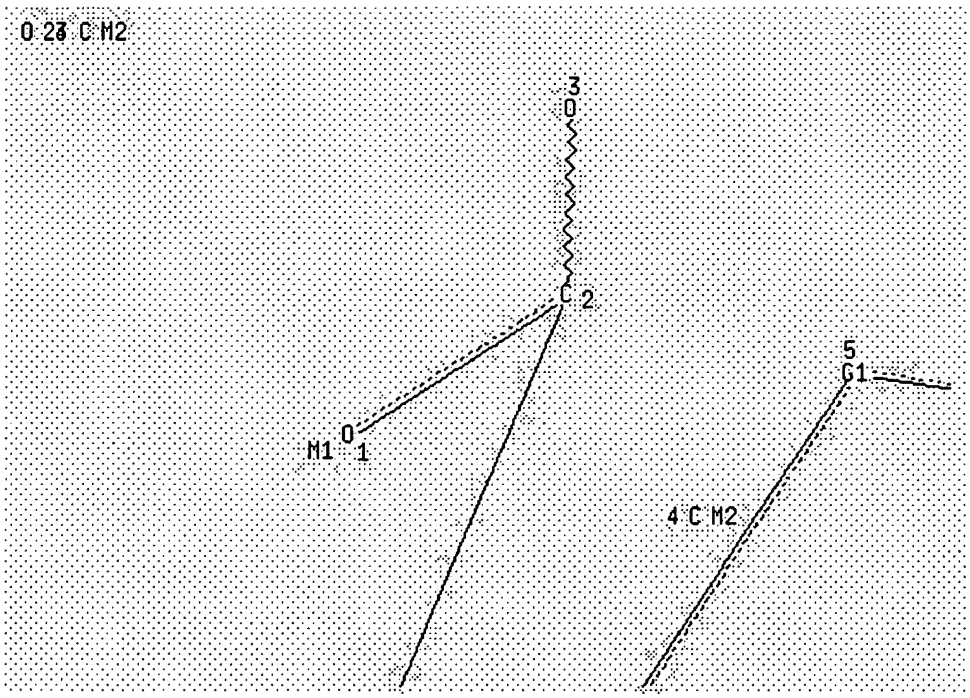
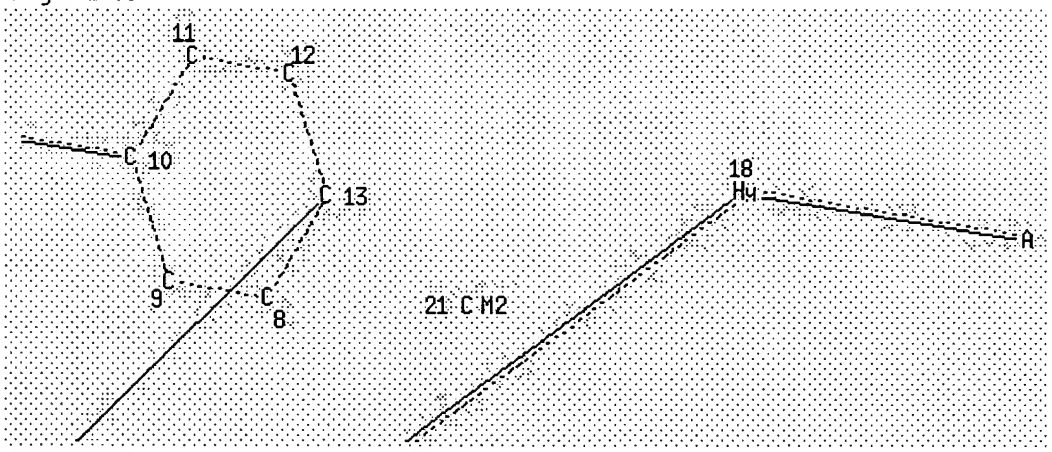


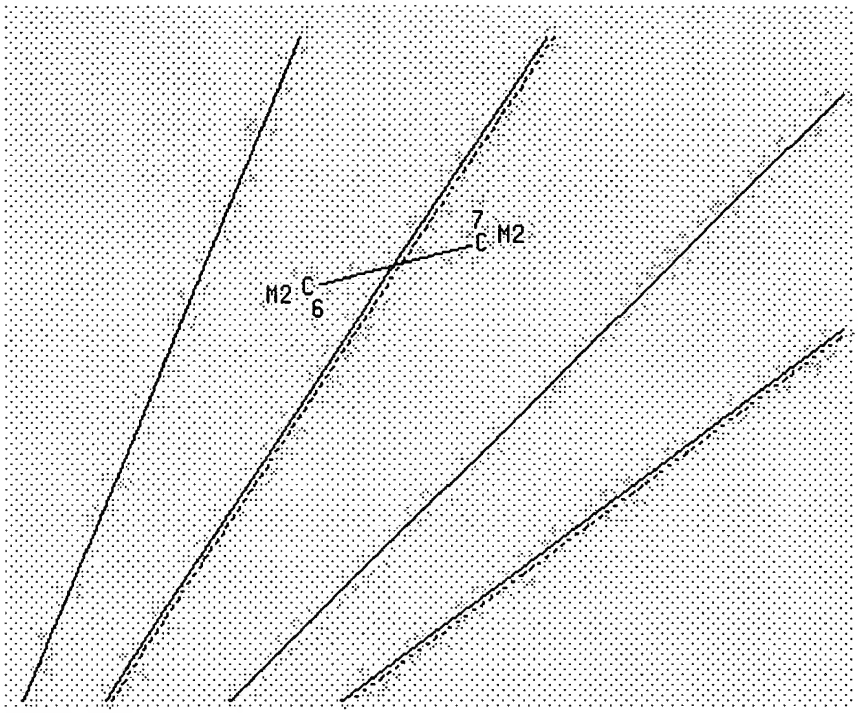
Page 1-A



Page 1-B

19

Page 1-C



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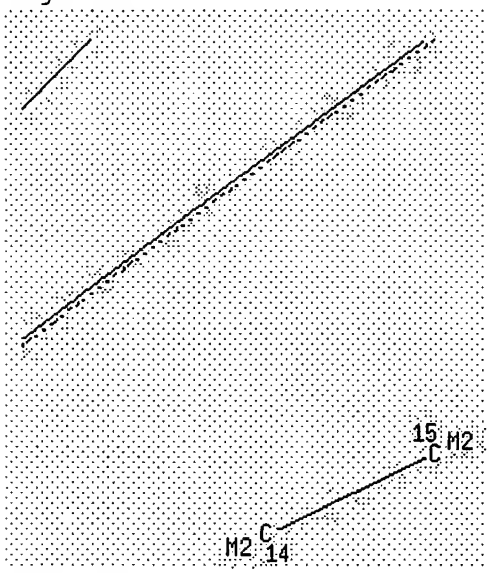

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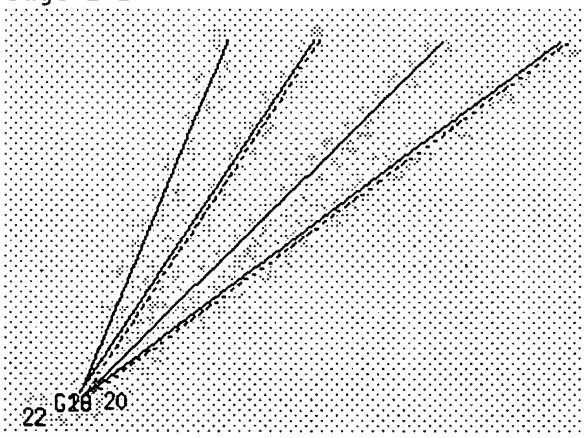

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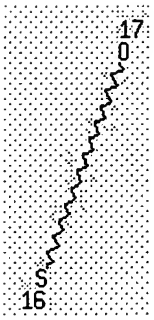

Page 3-B
VAR G1=23/24/6-20 6-10
REP G19=(1-2) 21-18 21-13
REP G20=(1-2) 4-2 4-5
NODE ATTRIBUTES:
HCOUNT IS M1 AT 1
HCOUNT IS M2 AT 4
HCOUNT IS M2 AT 6
HCOUNT IS M2 AT 7
HCOUNT IS M2 AT 14
HCOUNT IS M2 AT 15
HCOUNT IS M2 AT 21
HCOUNT IS M2 AT 24
NSPEC IS C AT 1
NSPEC IS C AT 2
NSPEC IS C AT 3
NSPEC IS C AT 4
NSPEC IS C AT 5
NSPEC IS C AT 6
NSPEC IS C AT 7
NSPEC IS R AT 8
NSPEC IS R AT 9
NSPEC IS R AT 10
NSPEC IS R AT 11
NSPEC IS R AT 12
NSPEC IS R AT 13
NSPEC IS C AT 14
NSPEC IS C AT 15
NSPEC IS C AT 16
NSPEC IS C AT 17
NSPEC IS C AT 18
NSPEC IS C AT 19
NSPEC IS C AT 20
NSPEC IS C AT 21
NSPEC IS C AT 22
DEFAULT MLEVEL IS ATOM
MLEVEL IS CLASS AT 1 2 3 4 6 7 14 15 16 17 19 21 23 24
DEFAULT ECLEVEL IS LIMITED
ECOUNT IS M1-X3 N AT 18

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS 24

STEREO ATTRIBUTES: NONE

=> s l21
SAMPLE SEARCH INITIATED 11:52:40 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 50376 TO ITERATE

```
  4.0% PROCESSED     2000 ITERATIONS                                0 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **INCOMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:       994134 TO  1020906
PROJECTED ANSWERS:               0 TO        0

L22           0 SEA SSS SAM L21

=>
Uploading structure

L23     STRUCTURE UPLOADED

=> d 123
L23 HAS NO ANSWERS
L23             STR

=> s 123
SAMPLE SEARCH INITIATED 11:54:12 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -   200149 TO ITERATE

  1.0% PROCESSED     2000 ITERATIONS                                0 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **INCOMPLETE**
                        BATCH   **INCOMPLETE**
PROJECTED ITERATIONS:      3976780 TO  4029180
PROJECTED ANSWERS:               0 TO        0

L24           0 SEA SSS SAM L23

=>
Uploading structure

L25     STRUCTURE UPLOADED

=> d 125
L25 HAS NO ANSWERS
L25             STR

=> s 125
SAMPLE SEARCH INITIATED 11:55:33 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -    14365 TO ITERATE

 13.9% PROCESSED     2000 ITERATIONS                                0 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:       280121 TO   294479
PROJECTED ANSWERS:               0 TO        0

L26           0 SEA SSS SAM L25
```

```
=> s l25 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 160.90 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 11:55:37 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   289093 TO ITERATE

100.0% PROCESSED   289093 ITERATIONS                          126 ANSWERS
SEARCH TIME: 00.00.01

L27         126 SEA SSS FUL L25

=> file hcaplus
COST IN U.S. DOLLARS                              SINCE FILE      TOTAL
                                                     ENTRY    SESSION
FULL ESTIMATED COST                                 167.35     388.97

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)        SINCE FILE      TOTAL
                                                     ENTRY    SESSION
CA SUBSCRIBER PRICE                                   0.00      -3.65

FILE 'HCAPLUS' ENTERED AT 11:55:42 ON 19 DEC 2005
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FILE COVERS 1907 - 19 Dec 2005  VOL 143 ISS 26
FILE LAST UPDATED: 18 Dec 2005  (20051218/ED)

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 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s l27
L28         126 L27

=> s l28 and bell, r?/au
          2688 BELL, R?/AU
L29          1 L28 AND BELL, R?/AU

=> d l29, ibib abs hitstr, 1

L29  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2005 ACS on STN
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Full Text | Citing References

```
ACCESSION NUMBER:         2004:2698  HCAPLUS
DOCUMENT NUMBER:          140:59519
TITLE:                    Preparation of (biphenylylalkoxy)- and
                          [(phenylpyridyl)alkoxy]-substituted phenylalkanoic
```

acids and phenoxyalkanoic acids as hPPAR activators for treatment of cardiovascular disease and related disorders

INVENTOR(S): Hamlett, Christopher Charles Frederick; **Bell, Richard**; Beswick, Paul John; Gosmini, Romain Luc Marie; King, Nigel Paul; Patel, Vipulkumar Kantibhai

PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA

SOURCE: PCT Int. Appl., 158 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

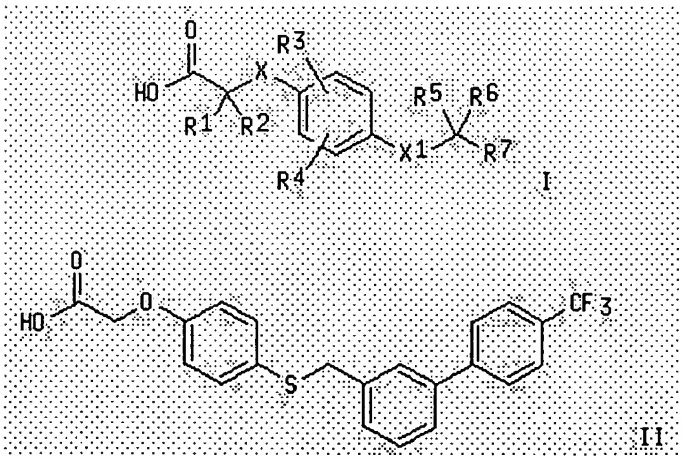
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004000315	A1	20031231	WO 2003-EP6415	20030618
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2487909	AA	20031231	CA 2003-2487909	20030618
EP 1513526	A1	20050316	EP 2003-738056	20030618
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003011931	A	20050405	BR 2003-11931	20030618
JP 2005534672	T2	20051117	JP 2004-514761	20030618
NO 2004005328	A	20050309	NO 2004-5328	20041203
PRIORITY APPLN. INFO.:			GB 2002-14149 A	20020619
			WO 2003-EP6415 W	20030618

OTHER SOURCE(S): MARPAT 140:59519

GI

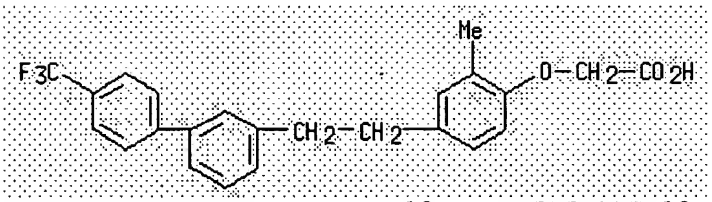


AB Title compds. I [wherein R1 and R2 = independently H or alkyl; X = O or (CH2)n; n = 0-2; R3 R4 = independently H, alkyl, OMe, CF3, allyl, or halo;

X1 = O, S, SO2, SO, or CH2; R5 and R6 = independently H, (halo)alkyl, or alkoxyalkyl; or CR5R6 = cycloalkyl; R7 = (un)substituted Ph or 6-membered heteroaryl; and pharmaceutically acceptable salts, solvates, and hydrolyzable esters thereof] were prepd. as human peroxisome proliferator activated receptor (hPPAR) activators. For example, a mixt. of 3-(bromomethyl)-4'-(trifluoromethyl)biphenyl, Et (4-mercapto-2-methylphenoxy)acetate, and polymer-supported diisopropylethylamine in DCM was stirred at room temp. overnight to give the thioether. Sapon. of the ester with aq. NaOH in THF and acidification afforded II. Compds. of the invention showed at least 50% activation of hPPARδ relative to the pos. control at concns. of 10-7 M or less. Thus, I and their pharmaceutical compns. are useful for the treatment of hPPAR mediated conditions, such as dyslipidemia, syndrome X, heart failure, hypercholesterolemia, cardiovascular disease, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidemia, obesity, anorexia bulimia, or anorexia nervosa (no data).

IT **638215-25-5P**, [[2-Methyl-4-[2-[4'-(trifluoromethyl)biphenyl-3-yl]ethyl]phenyl]oxy]acetic acid
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hPPAR activator; prepn. of (aryloxy)phenylalkanoic acids and (aryloxy)phenoxyalkanoic acids as hPPAR activators for treatment of cardiovascular disease and related disorders)

RN 638215-25-5 HCAPLUS
CN Acetic acid, [2-methyl-4-[2-[4'-(trifluoromethyl)[1,1'-biphenyl]-3-yl]ethyl]phenoxy]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 11:22:18 ON 19 DEC 2005)

FILE 'REGISTRY' ENTERED AT 11:22:30 ON 19 DEC 2005
L1 STRUCTURE UPLOADED
L2 24 S L1
L3 STRUCTURE UPLOADED
L4 43 S L3
L5 STRUCTURE UPLOADED
L6 12 S L5
L7 3264 S L5 FULL

FILE 'HCAPLUS' ENTERED AT 11:41:56 ON 19 DEC 2005
L8 37147 S L7
L9 3 S L8 AND BELL, R?/AU
L10 37144 S L8 NOT L9
L11 0 S L10 AND BESWICK, P?/AU
L12 0 S L10 AND GOSMINI, R?/AU
L13 0 S L10 AND GRIMES, R?/AU

```
L14             0 S L10 AND HAMLETT, C?/AU
L15             0 S L10 AND KING, N?/AU
L16             2 S L10 AND PATEL, V?/AU

     FILE 'HCAPLUS' ENTERED AT 11:46:49 ON 19 DEC 2005

     FILE 'REGISTRY' ENTERED AT 11:46:51 ON 19 DEC 2005
L17               STRUCTURE UPLOADED
L18             1 S L17
L19               STRUCTURE UPLOADED
L20             0 S L19
L21               STRUCTURE UPLOADED
L22             0 S L21
L23               STRUCTURE UPLOADED
L24             0 S L23
L25               STRUCTURE UPLOADED
L26             0 S L25
L27           126 S L25 FULL

     FILE 'HCAPLUS' ENTERED AT 11:55:42 ON 19 DEC 2005
L28           126 S L27
L29             1 S L28 AND BELL, R?/AU

=> s l28 not l29
L30         125 L28 NOT L29

=> s l30 and beswick, p?/au
             57 BESWICK, P?/AU
L31           0 L30 AND BESWICK, P?/AU

=> s l30 and gosmini, r?/au
             16 GOSMINI, R?/AU
L32           0 L30 AND GOSMINI, R?/AU

=> s l30 and grimes, r?/au
            557 GRIMES, R?/AU
L33           0 L30 AND GRIMES, R?/AU

=> s l30 and hamlett, c?/au
              2 HAMLETT, C?/AU
L34           0 L30 AND HAMLETT, C?/AU

=> s l30 and harlow, n?/au
              7 HARLOW, N?/AU
L35           0 L30 AND HARLOW, N?/AU

=> s l30 and patel, v?/au
           1058 PATEL, V?/AU
L36           0 L30 AND PATEL, V?/AU

=> d his

     (FILE 'HOME' ENTERED AT 11:22:18 ON 19 DEC 2005)

     FILE 'REGISTRY' ENTERED AT 11:22:30 ON 19 DEC 2005
L1                STRUCTURE UPLOADED
L2             24 S L1
L3                STRUCTURE UPLOADED
L4             43 S L3
L5                STRUCTURE UPLOADED
```

```
L6            12 S L5
L7          3264 S L5 FULL

     FILE 'HCAPLUS' ENTERED AT 11:41:56 ON 19 DEC 2005
L8         37147 S L7
L9             3 S L8 AND BELL, R?/AU
L10        37144 S L8 NOT L9
L11            0 S L10 AND BESWICK, P?/AU
L12            0 S L10 AND GOSMINI, R?/AU
L13            0 S L10 AND GRIMES, R?/AU
L14            0 S L10 AND HAMLETT, C?/AU
L15            0 S L10 AND KING, N?/AU
L16            2 S L10 AND PATEL, V?/AU

     FILE 'HCAPLUS' ENTERED AT 11:46:49 ON 19 DEC 2005

     FILE 'REGISTRY' ENTERED AT 11:46:51 ON 19 DEC 2005
L17              STRUCTURE UPLOADED
L18            1 S L17
L19              STRUCTURE UPLOADED
L20            0 S L19
L21              STRUCTURE UPLOADED
L22            0 S L21
L23              STRUCTURE UPLOADED
L24            0 S L23
L25              STRUCTURE UPLOADED
L26            0 S L25
L27          126 S L25 FULL

     FILE 'HCAPLUS' ENTERED AT 11:55:42 ON 19 DEC 2005
L28          126 S L27
L29            1 S L28 AND BELL, R?/AU
L30          125 S L28 NOT L29
L31            0 S L30 AND BESWICK, P?/AU
L32            0 S L30 AND GOSMINI, R?/AU
L33            0 S L30 AND GRIMES, R?/AU
L34            0 S L30 AND HAMLETT, C?/AU
L35            0 S L30 AND HARLOW, N?/AU
L36            0 S L30 AND PATEL, V?/AU

=> s l30 and pd < july 2002
      22609158 PD < JULY 2002
                 (PD<20020700)
L37          81 L30 AND PD < JULY 2002

=> d l37, ibib abs hitstr, 1-15

L37  ANSWER 1 OF 81  HCAPLUS  COPYRIGHT 2005 ACS on STN
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Full Text | Citing References

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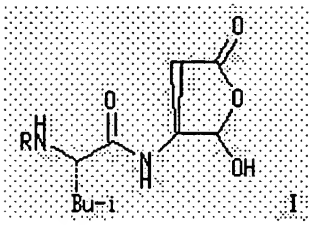
ACCESSION NUMBER:         2002:732410  HCAPLUS
DOCUMENT NUMBER:          138:170501
TITLE:                    Acyl dipeptides as reversible caspase inhibitors. Part
                          1: Initial Lead Optimization
AUTHOR(S):                Linton, Steven D.; Karanewsky, Donald S.; Ternansky,
                          Robert J.; Wu, Joe C.; Pham, Brian; Kodandapani,
                          Lalitha; Smidt, Robert; Diaz, Jose-Luis; Fritz,
                          Lawrence C.; Tomaselli, Kevin J.
CORPORATE SOURCE:         Idun Pharmaceuticals, Inc., San Diego, CA, 92121, USA
SOURCE:                   Bioorganic & Medicinal Chemistry Letters (2002),
```

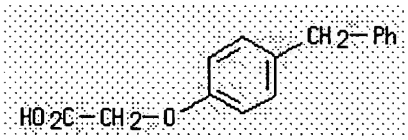
12(20), 2969-2971
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 138:170501
GI



AB Parallel synthesis of acyl dipeptides I (R = acyl) was used to explore the SAR of a peptidomimetic caspase inhibitor. The most potent compd. had nanomolar activity against caspases 1, 3, 6, 7, and 8.

IT **68671-02-3**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of acyl dipeptides as reversible caspase inhibitors)

RN 68671-02-3 HCAPLUS
CN Acetic acid, [4-(phenylmethyl)phenoxy]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

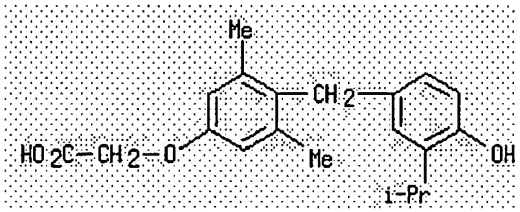
L37 ANSWER 2 OF 81 HCAPLUS COPYRIGHT 2005 ACS on STN
Full Text | Cited References

ACCESSION NUMBER: 2002:721656 HCAPLUS
DOCUMENT NUMBER: 138:280956
TITLE: A thyroid hormone antagonist that inhibits thyroid hormone action in vivo
AUTHOR(S): Lim, Wayland; Nguyen, Ngoc-Ha; Yang, Ha Yung; Scanlan, Thomas S.; Furlow, J. David
CORPORATE SOURCE: Sect. Neurobiol., Physiol, Behavior, University of California, Davis, CA, 95616-8519, USA
SOURCE: Journal of Biological Chemistry (**2002**), 277(38), 35664-35670
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

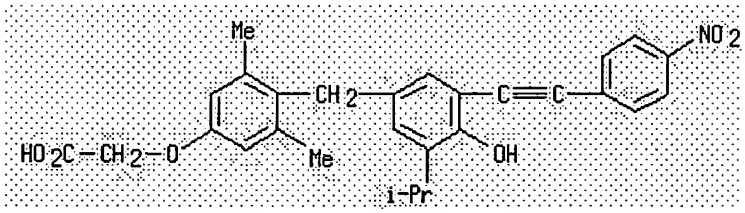
AB We have characterized the newly developed thyroid hormone antagonist NH-3 in both cell culture and in vivo model systems. NH-3 binds Xenopus laevis thyroid hormone receptors directly in vitro and induces a conformation distinct from agonist-bound receptors. Transcriptional activation of a thyroid hormone response element-contg. reporter gene is strongly inhibited by NH-3 in a dose-dependent manner. In addn., NH-3 prevents X. laevis thyroid hormone receptors from binding to the p160 family of

co-activators GRIP-1 and SRC-1 in a two-hybrid assay. To assess the potency of the compd. in vivo, we used induced and spontaneous X. laevis tadpole metamorphosis, a thyroid hormone-dependent developmental process. NH-3 inhibits thyroid hormone-induced morphol. changes in a dose-dependent manner and inhibits the up-regulation of endogenous thyroid hormone-responsive genes. Spontaneous metamorphosis is efficiently and reversibly arrested by NH-3 with at least the same effectiveness as the thyroid hormone synthesis inhibitor methimazole. Therefore, NH-3 is the first thyroid hormone antagonist to demonstrate potent inhibition of thyroid hormone action in both cell culture- and whole animal-based assays.

IT **211110-63-3**, GC-1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(comparison ligand; thyroid hormone antagonist that inhibits thyroid hormone action in vivo)
RN 211110-63-3 HCAPLUS
CN Acetic acid, [4-[[4-hydroxy-3-(1-methylethyl)phenyl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)



IT **447415-26-1**
RL: BSU (Biological study, unclassified); DMA (Drug mechanism of action); PAC (Pharmacological activity); BIOL (Biological study)
(thyroid hormone antagonist that inhibits thyroid hormone action in vivo)
RN 447415-26-1 HCAPLUS
CN Acetic acid, [4-[[4-hydroxy-3-(1-methylethyl)-5-[(4-nitrophenyl)ethynyl]phenyl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)



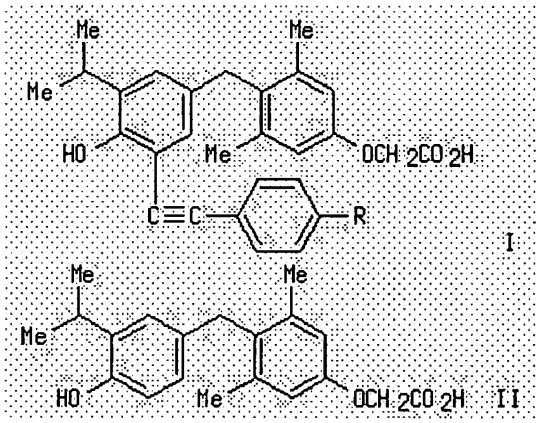
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 3 OF 81 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:457917 HCAPLUS
DOCUMENT NUMBER: 137:169293
TITLE: Rational Design and Synthesis of a Novel Thyroid Hormone Antagonist That Blocks Coactivator Recruitment
AUTHOR(S): Nguyen, Ngoc-Ha; Apriletti, James W.; Lima, Suzana T. Cunha; Webb, Paul; Baxter, John D.; Scanlan, Thomas S.
CORPORATE SOURCE: Program in Chemistry and Chemical Biology, Departments of Pharmaceutical Chemistry and Cellular and Molecular Pharmacology, University of California, San Francisco,

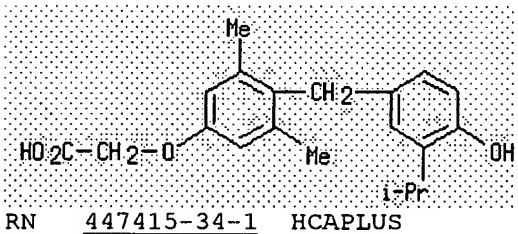
CA, 94143-0446, USA
SOURCE: Journal of Medicinal Chemistry (**2002**), 45(15), 3310-3320
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:169293
GI



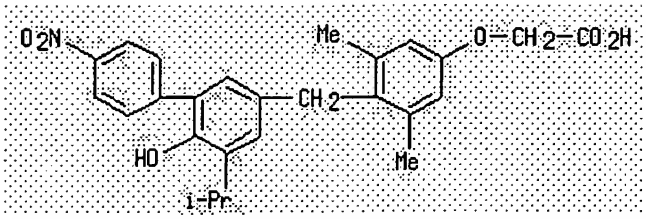
AB The authors report the design and synthesis of a novel series of phenylethynyl derivs. I [R = H, (CH2)4Me, NO2, NH2] sharing the halogen-free thyronine scaffold of GC-1 (II). I (R = NO2) is a T3 antagonist with negligible TR agonist activity and improved TR binding affinity and potency that allow for further characterization of its obsd. activity. Its ability to block TR-coactivator interactions appears to be the mechanism for antagonism. It will be a useful pharmacol. tool for further study of T3 signaling and TR function.

IT **211110-63-3**, GC-1 **447415-34-1**, GC 14
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. of phenylethynyl derivs. of GC-1 as thyroid hormone analogs and their binding activity towards thyroid hormone receptors)

RN 211110-63-3 HCAPLUS
CN Acetic acid, [4-[[4-hydroxy-3-(1-methylethyl)phenyl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)

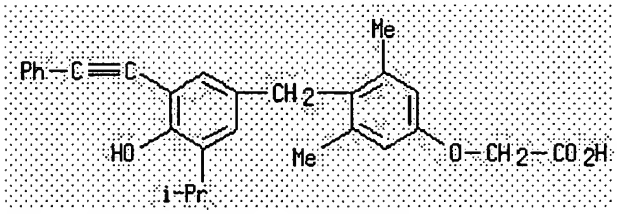


RN 447415-34-1 HCAPLUS
CN Acetic acid, [4-[[6-hydroxy-5-(1-methylethyl)-4'-nitro[1,1'-biphenyl]-3-yl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)



IT **447415-19-2P 447415-22-7P 447415-26-1P**
447415-29-4P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of phenylethynyl derivs. of GC-1 as thyroid hormone analogs and their binding activity towards thyroid hormone receptors)

RN 447415-19-2 HCAPLUS
CN Acetic acid, [4-[[4-hydroxy-3-(1-methylethyl)-5-(phenylethynyl)phenyl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)



RN 447415-22-7 HCAPLUS
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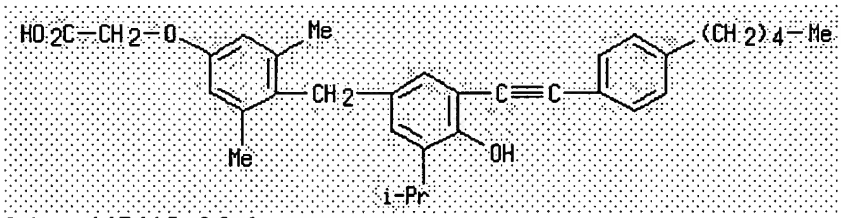
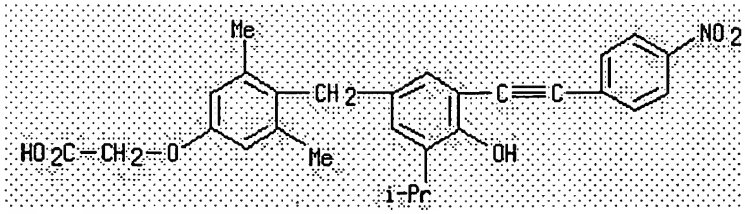
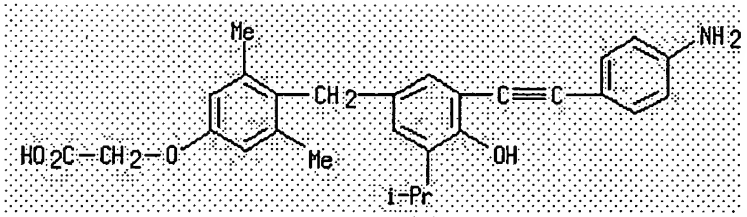


RN 447415-26-1 HCAPLUS
CN Acetic acid, [4-[[4-hydroxy-3-(1-methylethyl)-5-[(4-nitrophenyl)ethynyl]phenyl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)



RN 447415-29-4 HCAPLUS
CN Acetic acid, [4-[[3-[(4-aminophenyl)ethynyl]-4-hydroxy-5-(1-methylethyl)phenyl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

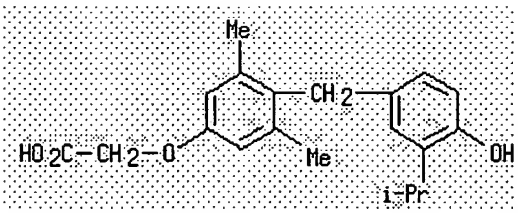
L37 ANSWER 4 OF 81 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | More References

ACCESSION NUMBER: 2002:266689 HCAPLUS
DOCUMENT NUMBER: 136:380441
TITLE: Deletion of the thyroid hormone receptor α1 prevents the structural alterations of the cerebellum induced by hypothyroidism
AUTHOR(S): Morte, Beatriz; Manzano, Jimena; Scanlan, Thomas; Vennstrom, Bjorn; Bernal, Juan
CORPORATE SOURCE: Instituto de Investigaciones Biomedicas Alberto Sols, Consejo Superior de Investigaciones Cientificas-Universidad Autonoma de Madrid, Madrid, 28029, Spain
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**2002**), 99(6), 3985-3989
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Thyroid hormone (T3) controls crit. aspects of cerebellar development, such as migration of postmitotic granule cells and terminal differentiation of Purkinje cells. T3 acts through nuclear receptors (TR) of two types, TRα1 and TRβ, that either repress or activate gene expression. We have analyzed the cerebellar structure of developing mice lacking the TRα1 isoform, which normally accounts for about 80% of T3 receptors in the cerebellum. Contrary to what was expected, granule cell migration and Purkinje cell differentiation were normal in the mutant mice. Even more striking was the fact that when neonatal hypothyroidism was induced, no alterations in cerebellar structure were obsd. in the mutant mice, whereas the wild-type mice showed delayed granule cell migration and arrested Purkinje cell growth. The results support the idea that repression by the TRα1 aporeceptor, and not the lack of thyroid hormone, is responsible for the hypothyroid phenotype. This conclusion was supported by expts. with the TRβ-selective compd. GC-1. Treatment of hypothyroid animals with T3, which binds to TRα1 and TRβ, prevents any defect in cerebellar structure. In contrast, treatment with GC-1, which binds to TRβ but not TRα1, partially corrects Purkinje cell differentiation but has no effect on granule cell migration. Our data indicate that thyroid hormone has a permissive effect on cerebellar granule cell migration through derepression by the TRα1 isoform.

IT **211110-63-3**, GC-1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(thyroid hormone receptor α1 deletion prevents structural alterations of cerebellum induced by hypothyroidism in developing mice)
RN 211110-63-3 HCAPLUS
CN Acetic acid, [4-[[4-hydroxy-3-(1-methylethyl)phenyl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)

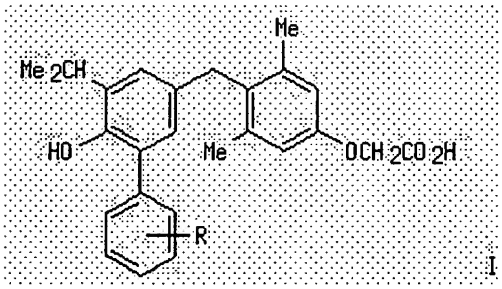


REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 5 OF 81 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:900234 HCAPLUS
DOCUMENT NUMBER: 136:340462
TITLE: Synthesis and biological activity of novel thyroid hormone analogues: 5'-aryl substituted GC-1 derivatives
AUTHOR(S): Chiellini, Grazia; Nguyen, Ngoc-Ha; Apriletti, James W.; Baxter, John D.; Scanlan, Thomas S.
CORPORATE SOURCE: Departments of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology, University of California, San Francisco, CA, 94143-0446, USA
SOURCE: Bioorganic & Medicinal Chemistry (2001), Volume Date 2002, 10(2), 333-346
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:340462
GI

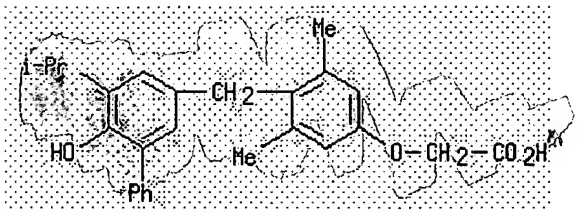


I

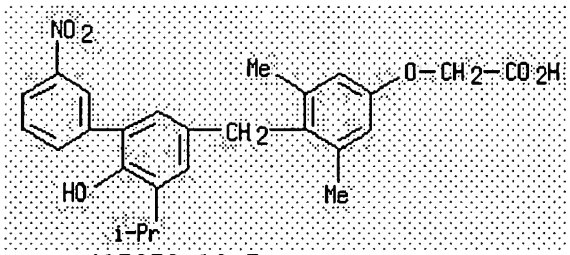
AB Biphenylmethylphenoxyacetic acids I [R = 4-NO2, 4-NHCH2CO2H, 4-NHCONHPh, 4-NHCH2C?CMe, 4-NH2, 3-NO2, 2-NO2, 4-CO2H, 4-CONH2, 4-NHC(:NH)NH2] were prepd. via arylation of the diphenylmethaneboronic acid. Substitution at the 5'-position decreased binding affinity, but retained TRβ-selectivity for most of the compds. Transactivation assays reveal that most of these compds. function as thyroid hormone agonists, but I [R = 4-NO2] antagonizes the response to thyroid hormone.

IT **417871-97-7P** **417872-05-0P** **417872-10-7P**
417872-14-1P **417872-18-5P** **417872-30-1P**
417872-38-9P **417872-45-8P** **417872-54-9P**
417872-67-4P **447415-34-1P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of biphenylmethylphenoxyacetic acids as thyroid hormone analogs)

RN 417871-97-7 HCAPLUS
CN Acetic acid, [4-[[6-hydroxy-5-(1-methylethyl)[1,1'-biphenyl]-3-yl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)



RN 417872-05-0 HCAPLUS
CN Acetic acid, [4-[[6-hydroxy-5-(1-methylethyl)-3'-nitro[1,1'-biphenyl]-3-yl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)



RN 417872-10-7 HCAPLUS
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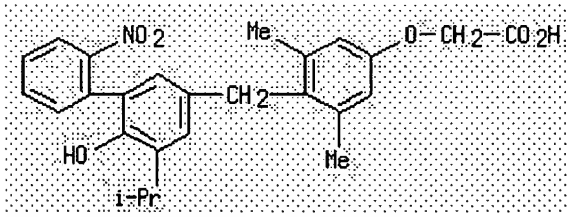
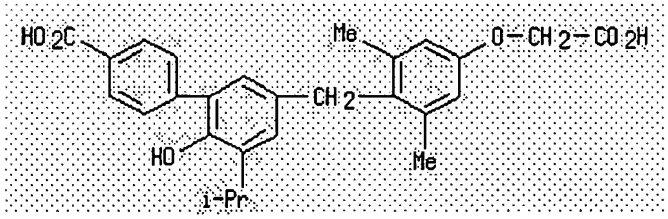
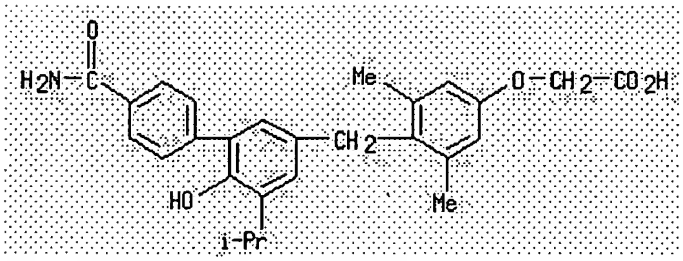


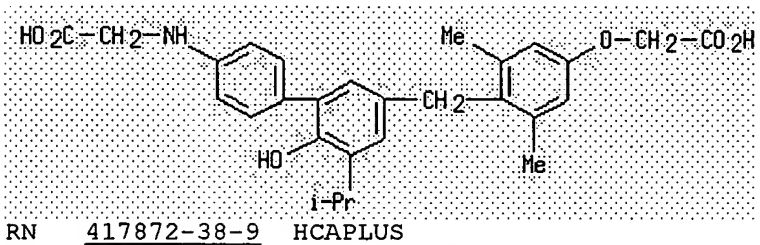
RN 417872-14-1 HCAPLUS
CN [1,1'-Biphenyl]-4-carboxylic acid, 5'-[[4-(carboxymethoxy)-2,6-dimethylphenyl]methyl]-2'-hydroxy-3'-(1-methylethyl)- (9CI) (CA INDEX NAME)



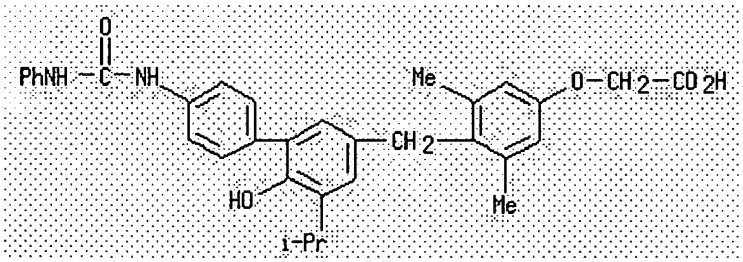
RN 417872-18-5 HCAPLUS
CN Acetic acid, [4-[[4'-(aminocarbonyl)-6-hydroxy-5-(1-methylethyl)[1,1'-biphenyl]-3-yl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)



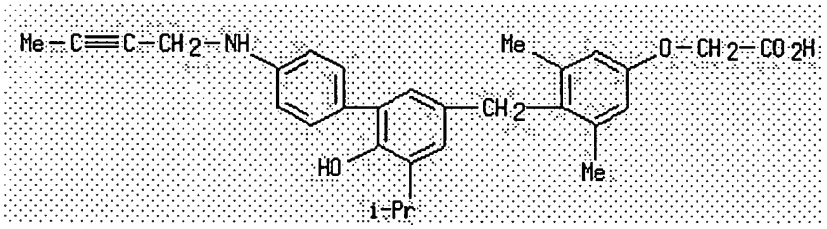
RN 417872-30-1 HCAPLUS
CN Glycine, N-[5'-[[4-(carboxymethoxy)-2,6-dimethylphenyl]methyl]-2'-hydroxy-3'-(1-methylethyl)[1,1'-biphenyl]-4-yl]- (9CI) (CA INDEX NAME)



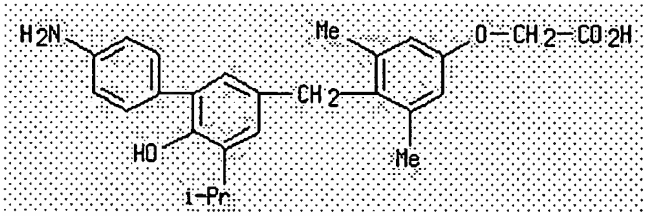
RN 417872-38-9 HCAPLUS
CN Acetic acid, [4-[[6-hydroxy-5-(1-methylethyl)-4'-[[(phenylamino)carbonyl]amino][1,1'-biphenyl]-3-yl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)



RN 417872-45-8 HCAPLUS
CN Acetic acid, [4-[[4'-(2-butynylamino)-6-hydroxy-5-(1-methylethyl)[1,1'-biphenyl]-3-yl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)

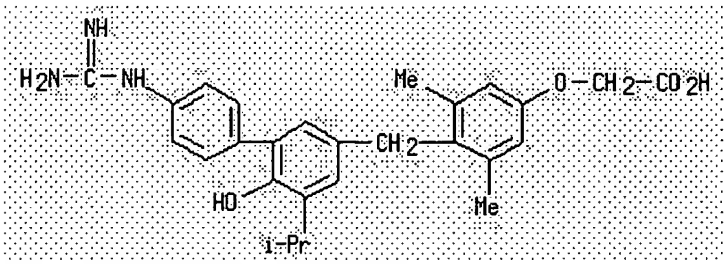


RN 417872-54-9 HCAPLUS
CN Acetic acid, [4-[[4'-amino-6-hydroxy-5-(1-methylethyl)[1,1'-biphenyl]-3-yl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)



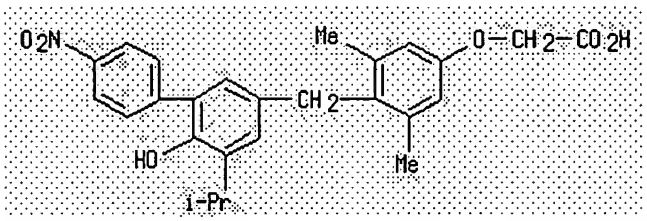
RN 417872-67-4 HCAPLUS

CN Acetic acid, [4-[[4'-[(aminoiminomethyl)amino]-6-hydroxy-5-(1-methylethyl)[1,1'-biphenyl]-3-yl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)



RN 447415-34-1 HCAPLUS

CN Acetic acid, [4-[[6-hydroxy-5-(1-methylethyl)-4'-nitro[1,1'-biphenyl]-3-yl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 6 OF 81 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:747805 HCAPLUS
DOCUMENT NUMBER: 135:273163
TITLE: Preparation of O-aryl glucosides as antidiabetic agents and SGLT2 inhibitors
INVENTOR(S): Washburn, William N.; Sher, Philip M.; Wu, Gang
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001074834	**A1**	**20011011**	**WO 2001-US10092**	**20010329**
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002111315	A1	20020815	US 2001-791512	20010223
US 6683056	B2	20040127		
CA 2404373	**AA**	**20011011**	**CA 2001-2404373**	**20010329**
EP 1268502	A1	20030102	EP 2001-922840	20010329

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

JP 2004500416	T2	20040108	JP 2001-572523		20010329
BR 2001009326	A	20040330	BR 2001-9326		20010329
NZ 520822	A	20050324	NZ 2001-520822		20010329
ZA 2002007030	A	20031202	ZA 2002-7030		20020902
NO 2002004642	A	20021121	NO 2002-4642		20020927
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			WO 2001-US10092	W	20010329

OTHER SOURCE(S): MARPAT 135:273163

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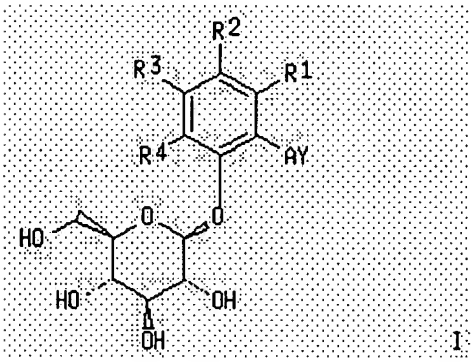


I

AB O-aryl glucosides I wherein Y is heteroaryl; A is -O(CH2)m, S, -NH(CH2)m, or (CH2)n where n is 0-3 and m is 0-2; and R1-R4 are independently H, OH, alkoxy, alkyl, halogen, two of R1-R4 together with the carbons to which they are attached can form an annelated five, six, or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms, were prepd. as antidiabetic agents and SGLT2 inhibitors. A method is also provided for treating diabetes and related diseases employing an SGLT2 inhibiting amt. of the above compd. alone or in combination with one, two or more other antidiabetic agents, and/or one, two or more hypolipidemic agents. Thus, I (R1-R4 = H, A = CH2, Y = C6H5-Me-4) was prepd. as antidiabetic and SGLT2 inhibitor (no data).

IT **363164-79-8P**

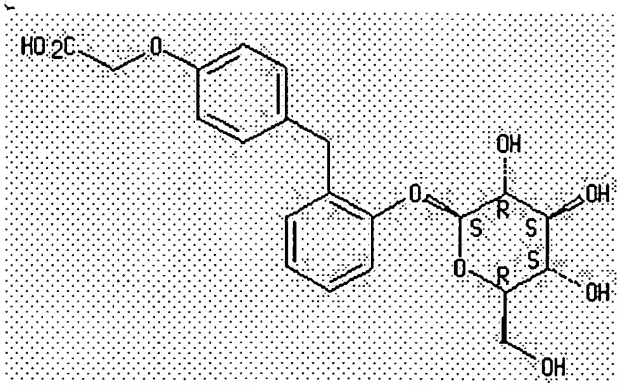
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of O-aryl glucosides as antidiabetic agents and SGLT2 inhibitors)

RN 363164-79-8 HCAPLUS

CN Acetic acid, [4-[[2-(β-D-glucopyranosyloxy)phenyl]methyl]phenoxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 7 OF 81 HCAPLUS COPYRIGHT 2005 ACS on STN

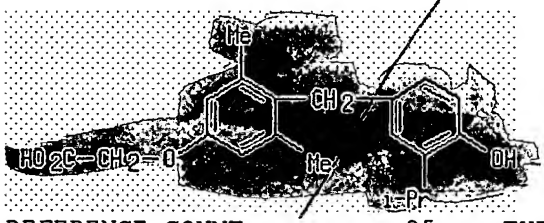
Full Text | Citing References

ACCESSION NUMBER: 2001:746604 HCAPLUS
DOCUMENT NUMBER: 136:145158
TITLE: A designed antagonist of the thyroid hormone receptor
AUTHOR(S): Yoshihara, H. A. I.; Apriletti, J. W.; Baxter, J. D.; Scanlan, T. S.
CORPORATE SOURCE: Departments of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology, University of California, San Francisco, CA, 94143-0446, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (**2001**), 11(21), 2821-2825
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An analog of the thyromimetic GC-1 bearing the same hydrophobic appendage as the estrogen receptor antagonist ICI-164,384 was prepd. While having reduced affinity for the thyroid hormone receptors compared to GC-1, it behaves in a manner consistent with a competitive antagonist in a transactivation assay.

IT **211110-63-3D**, GC 1, analogs
RL: PAC (Pharmacological activity); BIOL (Biological study)
(prepn. and structure activity relations of GC-1 analogs as antagonists of thyroid hormone receptor)

RN 211110-63-3 HCAPLUS
CN Acetic acid, [4-[[4-hydroxy-3-(1-methylethyl)phenyl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)



Better one found

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 8 OF 81 HCAPLUS COPYRIGHT 2005 ACS on STN

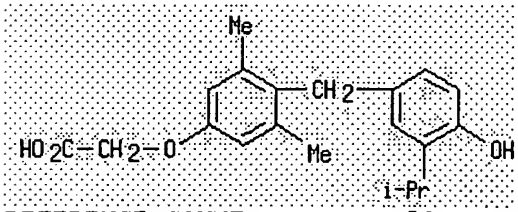
Full Text | Citing References

ACCESSION NUMBER: 2001:482817 HCAPLUS

DOCUMENT NUMBER: 135:205767
TITLE: Thyroid hormone-sympathetic interaction and adaptive thermogenesis are thyroid hormone receptor isoform-specific
AUTHOR(S): Ribeiro, Miriam O.; Carvalho, Suzy D.; Schultz, James J.; Chiellini, Grazia; Scanlan, Thomas S.; Bianco, Antonio C.; Brent, Gregory A.
CORPORATE SOURCE: Molecular Endocrinology Laboratory, Veterans Affairs Greater Los Angeles Healthcare System and Departments of Medicine and Physiology, UCLA School of Medicine, Los Angeles, CA, USA
SOURCE: Journal of Clinical Investigation (**2001**), 108(1), 97-105
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In newborns and small mammals, cold-induced adaptive (or nonshivering) thermogenesis is produced primarily in brown adipose tissue (BAT). Heat prodn. is stimulated by the sympathetic nervous system, but it has an abs. requirement for thyroid hormone. The authors used the thyroid hormone receptor-β-selective (TR-β-selective) ligand, GC-1, to det. by a pharmacol. approach whether adaptive thermogenesis was TR isoform-specific. Hypothyroid mice were treated for 10 days with varying doses of T3 or GC-1. The level of uncoupling protein 1 (UCP1), the key thermogenic protein in BAT, was restored by either T3 or GC-1 treatment. However, whereas interscapular BAT in T3-treated mice showed a 3.0 ?C elevation upon infusion of norepinephrine, indicating normal thermogenesis, the temp. did not increase (<0.5 ?C) in GC-1-treated mice. When exposed to cold (4 ?C), GC-1-treated mice also failed to maintain core body temp. and had reduced stimulation of BAT UCP1 mRNA, indicating impaired adrenergic responsiveness. Brown adipocytes isolated from hypothyroid mice replaced with T3, but not from those replaced with GC-1, had normal cAMP prodn. in response to adrenergic stimulation in vitro. The authors conclude that two distinct thyroid-dependent pathways, stimulation of UCP1 and augmentation of adrenergic responsiveness, are mediated by different TR isoforms in the same tissue.

IT **211110-63-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(thyroid hormone-sympathetic interaction and adaptive thermogenesis are thyroid hormone receptor isoform-specific)
RN 211110-63-3 HCAPLUS
CN Acetic acid, [4-[[4-hydroxy-3-(1-methylethyl)phenyl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

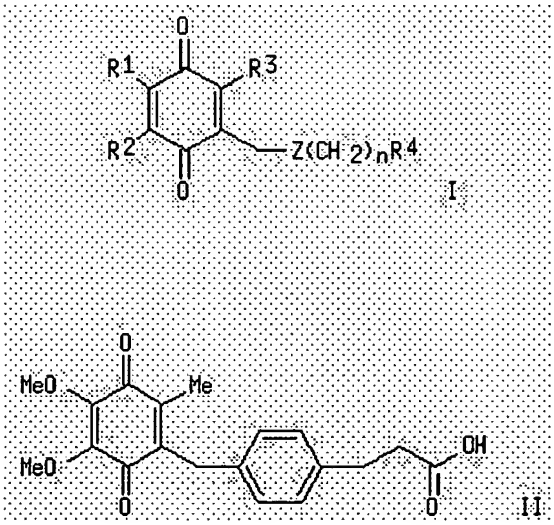
L37 ANSWER 9 OF 81 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:228738 HCAPLUS
DOCUMENT NUMBER: 134:252154
TITLE: Preparation and activity of dimethoxybenzoquinonemethylphenylalkylcarboxamide as NF-κB inhibitors useful for preventives or remedies ingredients for myocarditis, dilated cardiomyopathy, and heart failure
INVENTOR(S): Nunokawa, Youichi; Matsumori, Akira
PATENT ASSIGNEE(S): Suntory Limited, Japan
SOURCE: PCT Int. Appl., 214 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001021206	**A1**	**20010329**	**WO 2000-JP6364**	**20000918**
W: AU, CA, CN, HU, JP, KR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2350992	**AA**	**20010329**	**CA 2000-2350992**	**20000918**
AU 2000073154	**A5**	**20010424**	**AU 2000-73154**	**20000918**
EP 1132093	**A1**	**20010912**	**EP 2000-961066**	**20000918**
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6703421	B1	20040309	US 2001-856072	20010517
PRIORITY APPLN. INFO.:			JP 1999-264682 A	19990917
			WO 2000-JP6364 W	20000918

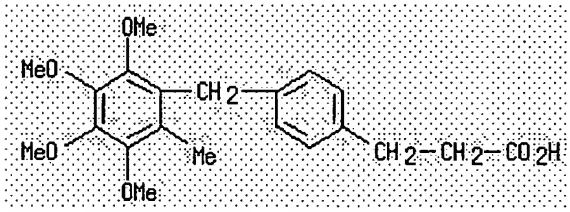
OTHER SOURCE(S): MARPAT 134:252154
GI



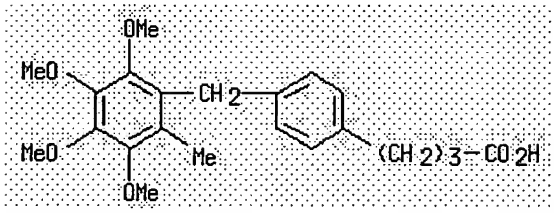
AB Title compds. [I; R1 = OCH3; R2 = OCH3; R3 = CH3; Z = 4-C6H4; R4 = COOH, CONMe2, CONHCH(CH3)2, CONH(CH2)2OH; n = CH2CH2] are prepd. as the active ingredient NF-κB inhibitors useful for Preventives or remedies ingredients for myocarditis, dilated cardiomyopathy, and hear failure. Thus, the title compd. II was prepd. and tested.

IT **245088-30-6P**, 3-[4-(2,3,4,5-Tetramethoxy-6-methylbenzyl)phenyl]propionic acid **245088-37-3P**, 4-[4-(2,3,4,5-Tetramethoxy-6-methylbenzyl)phenyl]-n-butyric acid
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and activity of dimethoxybenzoquinonemethylphenylalkylcarboxamide as NF-κB inhibitors useful for preventives or remedies ingredients for myocarditis, dilated cardiomyopathy, and heart failure)

RN 245088-30-6 HCAPLUS
CN Benzenepropanoic acid, 4-[(2,3,4,5-tetramethoxy-6-methylphenyl)methyl]- (9CI) (CA INDEX NAME)



RN 245088-37-3 HCAPLUS
CN Benzenebutanoic acid, 4-[(2,3,4,5-tetramethoxy-6-methylphenyl)methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 10 OF 81 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:184292 HCAPLUS
DOCUMENT NUMBER: 134:231960
TITLE: Hormone selectivity in thyroid hormone receptors
AUTHOR(S): Wagner, Richard L.; Huber, B. Russell; Shiau, Andrew K.; Kelly, Alex; Lima, Suzana T. Cunha; Scanlan, Thomas S.; Apriletti, James W.; Baxter, John D.; West, Brian L.; Fletterick, Robert J.
CORPORATE SOURCE: Department of Biochemistry and Biophysics, University of California, San Francisco, San Francisco, CA, 94143, USA
SOURCE: Molecular Endocrinology (**2001**), 15(3), 398-410
CODEN: MOENEN; ISSN: 0888-8809
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

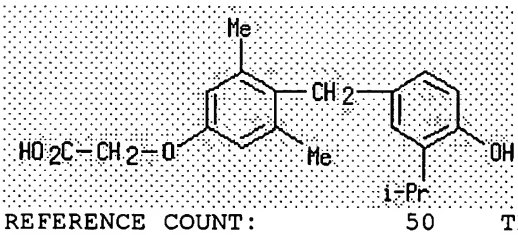
AB Sep. genes encode thyroid hormone receptor subtypes TRα (NR1A1) and TRβ (NR1A2). Products from each of these contribute to hormone action, but the subtypes differ in tissue distribution and physiol. response. Compds. that discriminate between these subtypes in vivo may be useful in treating important medical problems such as obesity and hypercholesterolemia. We previously detd. the crystal structure of the rat (r) TRα ligand-binding domain (LBD). In the present study, we

detd. the crystal structure of the rTRα LBD in a complex with an addnl. ligand, Triac (3,5, 3'-triiodothyroacetic acid), and two crystal structures of the human (h) TRβ receptor LBD in a complex with either Triac or a TRβ-selective compd., GC-1. The rTRα and hTRβ LBDs show close structural similarity. However, the hTRβ structures extend into the DNA-binding domain and allow definition of a structural "hinge" region of only three amino acids. The two TR subtypes differ in the loop between helixes 1 and 3, which could affect both ligand recognition and the effects of ligand in binding coactivators and corepressors. The two subtypes also differ in a single amino acid residue in the hormone-binding pocket, Asn (TRβ) for Ser (TRα). Studies here with TRs in which the subtype-specific residue is exchanged suggest that most of the selectivity in binding derives from this amino acid difference. The flexibility of the polar region in the TRβ receptor, combined with differential recognition of the chem. group at the 1-carbon position, seems to stabilize the complex with GC-1 and contribute to its β-selectivity. These results suggest a strategy for development of subtype-specific compds. involving modifications of the ligand at the 1-position.

IT **211110-63-3**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(hormone selectivity in thyroid hormone receptors)

RN 211110-63-3 HCAPLUS

CN Acetic acid, [4-[[4-hydroxy-3-(1-methylethyl)phenyl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 11 OF 81 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:67039 HCAPLUS
DOCUMENT NUMBER: 134:126317
TITLE: A subtype-selective thyromimetic designed to bind a mutant thyroid hormone receptor implicated in resistance to thyroid hormone
AUTHOR(S): Ye, Hai Fen; O'Reilly, Kathryn E.; Koh, John T.
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of Delaware, Newark, DE, 19716, USA
SOURCE: Journal of the American Chemical Society (**2001**), 123(7), 1521-1522
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors demonstrate that by using a known receptor agonists as a structural scaffold, potent (nanomolar active) hormone analogs can be rationally designed to complement a mutant form of the human thyroid hormone receptor beta (hTRβ) implicated in the genetic disease

resistance to thyroid hormone (RTH). The RTH-assocd. mutation, TRβ (R320C) exhibits a reduced affinity for triiodothyronine (T3). Furthermore, concns. of T3 required to significantly activate the mutant TRβ(R320C), impart an undesirable satg. response to TRα-mediated transactivation (EC50 = 0.14?0.24 nM). Therefore, compds. having high affinity and selectivity for mutant forms of TRβ over the α-subtype are sought for RTH therapy. The potent nonhalogenated thyromimetic GC1 shows a significantly reduced activity toward the mutant receptor TRβ(R320C) (EC50 = 37.7?10.8 nM) than to the TRβ(Wt) (EC50 3.67?1.1 nM) in cultured cells and is therefore no longer selective for the mutant β-subtype over TRα(Wt) (EC50 = 6.6?1.0 nM). On the basis of site-models generated from the coordinates of the T3/TRβ crystal structure, the authors designed the neutral alc. HY1 as a potential subtype-selective ligand for the mutant receptor hTRβ(R320C). Assays of transactivation function show that HY1 (EC50 = 7.01?3.0 nM) is 5-times more potent an agonist toward TRβ(R320C) than the parent compd. GC1, indicating that the authors' designed ligand was indeed more potent than GC1. Importantly, HY1 is also capable of eliciting substantial transactivation response from the mutant TRβ at concns. that show only partial activation of TRα (EC50 = 37.69?10.4 nM) and TRβ (EC50 = 32.05?8.7 nM). Although even greater levels of subtype-selectivity may be desirable, these data suggest that HY1 may have unique potential as a therapeutic capable of recovering activity from the mutant form of TRβ while potentially avoiding the undesirable side effects assocd. with TRα over stimulation. This work demonstrates that by making compensatory modifications to known hormone agonists, new, highly potent ligands can be made which are selective for mutant receptors implicated in human disease. Although in principle this general strategy may require a unique drug to be designed for each mutation assocd. with a particular disease, as demonstrated by this work on hTRβ, similar design strategies may be used to complement structurally similar mutations in related receptors.

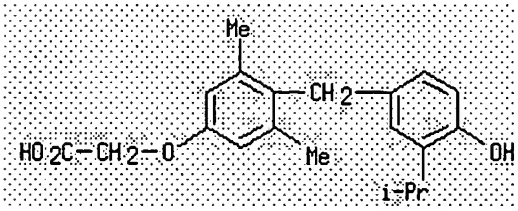
IT **211110-63-3**

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(subtype-selective thyromimetic designed to bind mutant thyroid hormone receptor implicated in resistance to thyroid hormone)

RN 211110-63-3 HCAPLUS

CN Acetic acid, [4-[[4-hydroxy-3-(1-methylethyl)phenyl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 12 OF 81 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2000:861461 HCAPLUS
DOCUMENT NUMBER: 134:32764
TITLE: Method of treating hair loss using diphenylmethane derivatives
INVENTOR(S): Zhang, Lixin Lilly; Youngquist, Robert Scott
PATENT ASSIGNEE(S): Procter and Gamble Company, USA
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

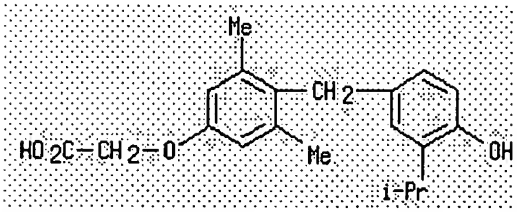
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000072813	**A1**	**20001207**	**WO 2000-US5254**	**20000301**
W: AU, BR, CA, CN, JP, KR, MX, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2374266	**AA**	**20001207**	**CA 2000-2374266**	**20000301**
AU 2000035078	**A5**	**20001218**	**AU 2000-35078**	**20000301**
EP 1185231	**A1**	**20020313**	**EP 2000-913678**	**20000301**
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2003500433	T2	20030107	JP 2000-620925	20000301
US 6680344	B1	20040120	US 2002-980407	20020329
PRIORITY APPLN. INFO.:			US 1999-137024P	P 19990601
			WO 2000-US5254	W 20000301

OTHER SOURCE(S): MARPAT 134:32764

AB The present disclosure describes methods for treating hair loss in mammals, including arresting and/or reversing hair loss and promoting hair growth. The methods comprise administering a cardiac-sparing diphenylmethane deriv. and a pharmaceutically-acceptable carrier. A topical compn. contained (3,5-dimethyl-4-(4'-hydroxy-3'isopropylbenzyl)phenoxy)acetic acid 5, EtOH 97, propylene glycol 19, and di-Me isosorbide 19%. A human male subject suffering from male pattern baldness was treated by the above formulation.

IT **211110-63-3**
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diphenylmethane derivs. for treating hair loss)

RN 211110-63-3 HCAPLUS
CN Acetic acid, [4-[[4-hydroxy-3-(1-methylethyl)phenyl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 13 OF 81 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

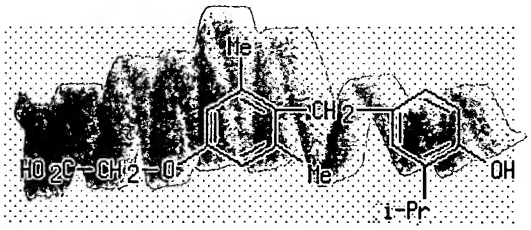
ACCESSION NUMBER: 2000:832454 HCAPLUS

DOCUMENT NUMBER: 134:207586
TITLE: Improved synthesis of the iodine-free thyromimetic GC-1
AUTHOR(S): Chiellini, G.; Nguyen, N.-H.; Yoshihara, H. A. I.; Scanlan, T. S.
CORPORATE SOURCE: Departments of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology, University of California, San Francisco, CA, 94143-0446, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2000), 10(23), 2607-2611
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:207586

AB Synthesis of the thyroid hormone receptor β-selective thyromimetic GC-1, [3,5-dimethyl-4-(4-hydroxy-3-isopropylbenzyl)phenyloxy]acetate, was improved using methoxymethyl (MOM) and triisopropylsilyl (TiPS) substituents as phenolic protecting groups. The new synthetic route is adaptable to analog design.

IT **211110-63-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of thyromimetic GC-1)

RN 211110-63-3 HCAPLUS
CN Acetic acid, [4-[[4-hydroxy-3-(1-methylethyl)phenyl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 14 OF 81 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2000:603809 HCAPLUS
DOCUMENT NUMBER: 133:233130
TITLE: The thyroid hormone receptor-β-selective agonist GC-1 differentially affects plasma lipids and cardiac activity
AUTHOR(S): Trost, Susanne U.; Swanson, Eric; Gloss, Bernd; Wang-Iverson, David B.; Zhang, Hongjiang; Volodarsky, Tanya; Grover, Gary J.; Baxter, John D.; Chiellini, Grazia; Scanlan, Thomas S.; Dillmann, Wolfgang H.
CORPORATE SOURCE: Department of Medicine, University of California, San Diego, CA, 92093-0618, USA
SOURCE: Endocrinology (2000), 141(9), 3057-3064
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Thyroid hormones influence the function of many organs and mediate their diverse actions through two types of thyroid hormone receptors, TRα and TRβ. Little is known about effects of ligands that

preferentially interact with the two different TR subtypes. In the current study the comparison of the effects of the novel synthetic TRβ-selective compd. GC-1 with T3 at equimolar doses in hypothyroid mice revealed that GC-1 had better triglyceride-lowering and similar cholesterol-lowering effects than T3. T3, but not GC-1, increased heart rate and elevated mRNA levels coding for the If channel (HCN2), a cardiac pacemaker that was decreased in hypothyroid mice. T3 had a larger pos. inotropic effect than GC-1. T3, but not GC-1, normalized heart and body wts. and mRNAs of myosin heavy chain α and β and the sarcoplasmic reticulum ATPase (Serca2). Addnl. dose-response studies in hypercholesteremic rats confirmed the preferential effect of GC-1 on TRβ-mediated parameters by showing a much higher potency to influence cholesterol and TSH than heart rate. The preferred accumulation of GC-1 in the liver vs. the heart probably also contributes to its marked lipid-lowering effect vs. the absent effect on heart rate. These data indicate that GC-1 could represent a prototype for new drugs for the treatment of high lipid levels or obesity.

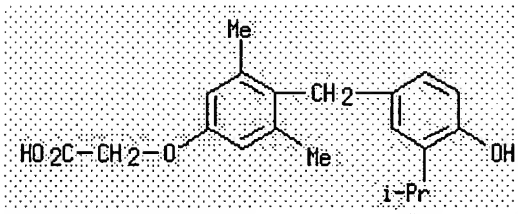
IT **211110-63-3**

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(thyroid hormone receptor-β-selective agonist GC-1 differentially affects plasma lipids and cardiac activity)

RN 211110-63-3 HCAPLUS

CN Acetic acid, [4-[[4-hydroxy-3-(1-methylethyl)phenyl]methyl]-3,5-dimethylphenoxy]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 15 OF 81 HCAPLUS COPYRIGHT 2005 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2000:87994 HCAPLUS

DOCUMENT NUMBER: 132:245841

TITLE: Structure-Activity Relationship Studies on 1-[2-(4-Phenylphenoxy)ethyl]pyrrolidine (SC-22716), a Potent Inhibitor of Leukotriene A4 (LTA4) Hydrolase

AUTHOR(S): Penning, Thomas D.; Chandrakumar, Nizal S.; Chen, Barbara B.; Chen, Helen Y.; Desai, Bipin N.; Djuric, Stevan W.; Docter, Stephen H.; Gasiecki, Alan F.; Haack, Richard A.; Miyashiro, Julie M.; Russell, Mark A.; Yu, Stella S.; Corley, David G.; Durley, Richard C.; Kilpatrick, Brian F.; Parnas, Barry L.; Askonas, Leslie J.; Gierse, James K.; Harding, Elizabeth I.; Highkin, Maureen K.; Kachur, James F.; Kim, Suzanne H.; Krivi, Gwen G.; Villani-Price, Doreen; Pyla, E. Yvonne; Smith, Walter G.; Ghoreishi-Haack, Nayereh S.

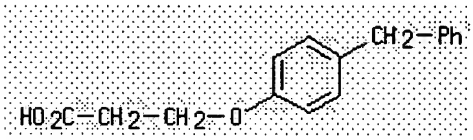
CORPORATE SOURCE: Departments of Medicinal Chemistry Structure-Activity Screening Program Inflammatory Diseases Research and Molecular Pharmacology Searle Research and Development, Monsanto Company, Skokie, IL, 60077, USA

SOURCE: Journal of Medicinal Chemistry (2000), 43(4), 721-735
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Leukotriene B4 (LTB4) is a pro-inflammatory mediator that has been implicated in the pathogenesis of a no. of diseases including inflammatory bowel disease (IBD) and psoriasis. Since the action of LTA4 hydrolase is the rate-limiting step for LTB4 prodn., this enzyme represents an attractive pharmacol. target for the suppression of LTB4 prodn. From an inhouse screening program, SC-22716 (1-[2-(4-phenylphenoxy)ethyl]pyrrolidine) was identified as a potent inhibitor of LTA4 hydrolase. Structure-activity relationship (SAR) studies around this structural class resulted in the identification of a no. of novel, potent inhibitors of LTA4 hydrolase, several of which demonstrated good oral activity in a mouse ex vivo whole blood assay.

IT **183719-26-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of and leukotriene A4 hydrolase inhibition by [(phenylphenoxy)ethyl]pyrrolidine analogs)

RN 183719-26-8 HCAPLUS
CN Propanoic acid, 3-[4-(phenylmethyl)phenoxy]- (9CI) (CA INDEX NAME)



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